

ANEMIA IN CENTRAL-ASIA PRE-SCHOOL CHILDREN: DEFINITION, RISK  
FACTORS AND EVALUATION OF HOME FORTIFICATION INTERVENTION

A Dissertation

Presented to the Faculty of the Graduate School

of Cornell University

in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

by

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August 2009

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# ANEMIA IN CENTRAL-ASIA PRESCHOOL CHILDREN: DEFINITION, RISK FACTORS AND EVALUATION OF HOME FORTIFICATION INTERVENTION

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**INTRODUCTION:** Anemia has been a major public health problem for pre-school children in Asia for decades. This dissertation is concerned with understanding the persistent public health problem of anemia in Central Asia. First, by modeling the relationship between hemoglobin and altitude, we develop an Asian based high-altitude correction factor for hemoglobin to accurately identify anemia. Second we examine the risks for anemia in a group of pre-school aged children in the Central Asian Republic of Kyrgyzstan to gain insight into the possible causes of anemia. Finally, we evaluate the cost-effectiveness of a home-based fortification method 'Sprinkles' to treat and prevent anemia in Central Asian preschoolers.

**DESIGN:** For the first analysis, Demographic and Health Survey data from women 15-49 and children 6 to 36 months old were used. Data for the second and third analyses were taken from a random sample of children 6 to 36 months residing in the Naryn region of the Central Kyrgyzstan. Cost data for the third study were collected retrospectively and combined with the results of the impact of Sprinkles on hemoglobin levels to produce the cost-effectiveness ratio of the cost per child per 1g/L change in hemoglobin.

**RESULTS:** The Asian-based altitude correction factors for hemoglobin produced more moderate adjustments, above 1000 meters, than correction factors derived based on non-Asian populations. Risk factors associated with anemia included several dietary variables as well as socio-demographic variables. Nearly two-thirds of the children had some level of anemia, 6% of which was severe. Finally, the cost of a

weekly dosage of Sprinkles per child was \$8.16 and the cost effectiveness was \$1.36 per child per 1 g/L change in hemoglobin.

**CONCLUSIONS:** Monitoring and evaluation of anemia in Central Asia should begin with an Asian-based correction factor for altitude to identify the prevalence of anemia. Risk factors associated with anemia in Kyrgyz preschool children were age, intake of meat, breast-milk, fruit and biscuits. Anemia risk was highest among younger children less than 24 months old. Further, a weekly dosage of Sprinkles is a cost-effective method of delivering iron to central Asian children to reduce or prevent anemia.

## BIOGRAPHICAL SKETCH

Avril was born in Kingston Jamaica. At the age of 11 she immigrated to Canada with her family. Throughout high school she enjoyed studying music and the theatre and only became interested in the sciences while attending the University of Toronto. After obtaining a Bachelors of Science in Biology and English and working as an Evoked Potentials Technician, she enrolled in the Masters of Science program in Nutrition at Howard University in Washington DC. Three years later she left for Goundam, Mali to build a nutrition program within the context of a food security project. Eight years later, after working as a Nutrition Program Manager in East Africa and Asia, she enrolled in the Program in International Nutrition in the Division of Nutritional Sciences at Cornell University. Avril currently works at MEASURE Demographic and Health Survey.

*In the words of the immortal negro poet Bob Marley, "Who Jah bless, no one curse." I have been blessed since my birth with the family I was born into and the friends and colleagues I have encountered. I give thanks for my mother, Gwendolyn Mcdougal who, without the resources to continue beyond a primary school education, continually moved her family forward with vision and fearlessness. I am appreciative of my father's never-ending dedication to his family and the dimples he gave to us all. My three brothers, Louis, Devon and Maurice have been my protectors and mentors and set the standard for how to "live good amongst people". I am thankful for my sister Sherine who has a capacity for love and kindness that is rare. To my nieces and nephews, numbers 1 to 10, who will probably never read this, you have been my strongest motivation throughout the pursuit of my doctoral degree.*

*In addition to my family, I thank my friends Edward Pussar, Kelly Puryear, Elise Braithwaite, Terry Victor, Gary Oates and Veronica Mahiga who have listened and laughed with me. For my special friend and partner Kevin Charles, I thank the universe for the gift of you, and the gifts you give me daily. Thanks for culturing me up!*

## ACKNOWLEDGMENTS

Throughout the production of this dissertation I was given considerable support and guidance from my friends and colleagues. I am grateful to my doctoral committee for their suggestions throughout my graduate studies. In particular, I acknowledge the contributions of Professor Rebecca Stoltzfus, my committee chair, who with grace and patience guided me to its completion. I thank Professors Edward Frongillo, Jere Haas and Donald Kenkel whose insights contributed significantly to my research:

In addition to my doctoral committee, I wish to thank Francoise Vermeulen and the Cornell Statistical Consulting Team for their kindness and support. I would also like to acknowledge the students and professors at Cornell who provided me with support and feedback that helped me to complete this dissertation. For the friendship and perspective of my Cornell colleagues Tafadzwa Mandimika, Nkosinathi Mbuya, Joseph Mensah-Homiah, Mohamed Ag Ayoya and Simeon Nanama I am grateful. Also, I would like to thank my collaborators at the Sprinkles Global Health initiative and the Swiss Red Cross Kyrgyzstan for their support.

A special thanks to Jeff Diver, Janet McCue and the staff at Mann Library for their dedication to provide excellent services to students. Finally, I thank Dr. P. Stanley Yoder for his perspectives, help and kindness.

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## CHAPTER 1

### INTRODUCTION

#### ***1.1 JUSTIFICATION***

Anemia continues to be a highly prevalent and unrelenting nutritional problem worldwide. After decades of public health actions, nearly half of the world's preschool aged children are anemic<sup>1</sup>. In Asia, where 47.7% of infants and young children are anemic, there is an urgent need for new strategies that are effective in preventing and controlling anemia in the long term.

Three important stages in the prevention and control of anemia are the definition of anemia, the identification of risk factors associated with anemia and the development of interventions that treat and control anemia. A hemoglobin concentration cut-off value, below which individuals are classified as anemic, is the most common method used to define anemia. Normal hemoglobin levels vary based on genetic or environmental factors. Before applying a cut-off to classify an individual as anemic and determine population prevalence, it is important to adjust hemoglobin levels for these factors to avoid misclassification<sup>1, 5, 14, 53, 64</sup>. Correctly adjusted hemoglobin levels can then be used not only to define prevalence but to identify those at the highest risk and to evaluate the effectiveness of interventions that may prevent or control anemia.

The three studies presented in this dissertation are linked through a common focus on the problem of anemia in Asia. The order in which they are presented parallels the steps taken in an approach to the problem of anemia: definition, assessment and prevention. The first study is focused on the definition of anemia. In this analysis we challenge the concept of a universal human hematological response to chronic hypobaric hypoxia and model the relationship between hemoglobin concentrations and altitude for Asian populations. Consequently, we develop

adjustments that can be used to correct altitude-induced variations in hemoglobin levels in life-long high altitude Asian residents before defining anemia. The second study is focused on the assessment of anemia. In this investigation, we assess the prevalence, associations and risk of anemia in a sample of pre-school aged children residing in Central Asia. The third study is focused on the prevention and control of anemia. We analyze the cost-effectiveness of an iron intervention program that used Sprinkles to prevent and control anemia in pre-school children in the Central Asian Republic of Kyrgyzstan. Our overall conclusions bring together the important findings from all 3 studies and implications for the prevention and treatment of anemia in pre-school children in Central-Asia.

## ***1.2 Organization of Dissertation***

This thesis is divided into 5 chapters. This first chapter serves as a general introduction to the thesis providing both justification for the research as well as a methodological background; the second details the approach used for the derivation of an Asia-specific altitude correction factor for hemoglobin; the third characterizes the epidemiology of anemia in Kyrgyz preschool children; the fourth paper presents the analysis of the cost and cost-effectiveness of the Kyrgyz Sprinkles program for the prevention and reduction of anemia in children 6 to 36; the final chapter provides overall conclusions and recommendations based on overall findings.

## ***1.3. Background***

### ***1.3.1 Anemia in Preschool Children***

A gap between iron requirements and meeting those requirements through adequate intake and absorption occurs between 6 and 24 months of age. This is the most important factor contributing to the high prevalence of iron deficiency anemia (IDA) in infants and young children in resource-poor nations of Africa and Asia<sup>4-7</sup>.

After the first 6 months of age, with depleted iron stores, infants rely on breast milk and complementary foods to support their accelerated growth and development<sup>7-9</sup>. Breast milk contributes little to requirements and children in developing countries consume gruels that are low in iron content and bioavailability. These gruels are often of thin consistency and consumed too infrequently to establish adequate iron intake<sup>9-11</sup>. Further, if these complementary foods are consumed with breast milk, they may reduce the bioavailability of iron in breast-milk as well<sup>9-12</sup>. Bridging this gap between iron taken in and absorbed and iron requirements by providing preschoolers with supplemental iron to ensure proper physical and cognitive development<sup>6-13</sup> would be a crucial step toward eliminating IDA in infants and children in developing countries.

### *1.3.2. Treating and Preventing Anemia in Infants and Young Children*

There is an urgent need for low cost methods that are effective in delivering iron to infants and young children in the form of fortified complementary foods or supplements<sup>13-16</sup>. Currently food fortification and iron supplementation are the main tools used to address IDA in infants and young children in developing countries<sup>13-16</sup>. Fortification has been successful in improving iron status in children in developed nations where populations have access to fortified infant foods such as formula or cereals<sup>14</sup>. However, in developing countries, there have been constraints to successful implementation. Centralized fortification is often used and it is not feasible to fortify the cereal based staples foods that are found in the most common locally consumed complementary foods<sup>8, 15-16</sup>. In addition, with relatively high requirements, children cannot consume adequate amounts of a fortified food to properly address deficiency<sup>9, 17</sup>. Related to this, the more desirable forms of iron cannot be used for fortification and other forms that are amenable are less well absorbed<sup>18-19</sup>. Lastly, fortification is inaccessible to the poorest and most vulnerable.

Relative to the more long-term strategy of fortification, supplementation has been viewed as efficacious and rapid in treating and preventing IDA since it can be targeted specifically to high-risk groups such as infants<sup>5-6,16,20</sup>. Efficacy trials have demonstrated that supplementation improves iron status in infants and children<sup>19</sup>. However, in large-scaled supplementation programs, the effectiveness of supplementation has been difficult to demonstrate<sup>15, 21</sup>. Barriers to supplementation include compliance and coverage<sup>15</sup>. These two components depend on the availability of supplements that are of quality and provide few side effects as well as adequate resources for both provider and recipients<sup>15</sup>. Finding the right supplement involves determining the appropriate balance between the cost of delivery, ease of use and compliance<sup>5, 16</sup>. ***Given the persistence of anemia in infants and children over the past few decades and the limitations of fortification and supplementation, the need for new, cost-effective strategies proven to reduce anemia in infants and children is urgent.***

### *1.3.3 Sprinkles*

Innovative approaches to overcoming barriers to iron supplementation and enhancing the intake of bio-available iron are needed to address the problem of IDA. One new approach is Sprinkles, ferrous fumarate microencapsulated in a soya-based hydrogenated lipid that has been introduced as a home-fortification approach to anemia reduction<sup>22-23</sup>. Sprinkles were developed to address constraints related to adherence encountered during program implementation. Packaged in single-dose sachets, Sprinkles can be added to homemade foods to increase nutritional content with minimal changes in the taste, texture or color of foods<sup>22-23</sup>. From the innovator's perspectives, these single-dose sachets are cheap (0.10 USD per sachet per child), easy to use, store and transport. Further, the iron in Sprinkles are well absorbed in children

who are iron deficient (4.5%) and iron deficient with anemia (8.3%)<sup>25</sup>; have none of the gastrointestinal discomforts, staining of the teeth and unpleasant taste associated with the already available iron drops and are thus more acceptable<sup>24,26-28</sup>.

This new method of delivering iron has been found as efficacious as iron drops in the treatment of anemia in infants and young children<sup>22-23, 29-32</sup>. The first randomized controlled studies in Ghana tested the efficacy of Sprinkles on treating anemia, improving zinc status, as well as preventing anemia recurrence. First, for two months, a group of 557 anemic (hemoglobin 70-99g/L) children aged 6 to 18 months were given daily dosages of Sprinkles containing 80 mg of elemental iron (Fe) plus ascorbic acid (50 mg). Their anemia status was compared to a control group who received drops of ferrous sulfate (40 mg of elemental iron) 3 times per day. Treatment with Sprinkles resulted in an increase in hemoglobin (Hb) in 58% of children compared to 56% of the group consuming drops.

Next, regarding Sprinkles and zinc status, plasma zinc concentration as well as Hb and serum ferritin (Sf) were measured in 304 Ghanaian children averaging  $10.3 \pm 2.5$  months old before and after a 2 month treatment period. One group of children received sachets of Sprinkles containing 80 mg of Fe and 10 mg zinc (Zn) and another group received Sprinkles only. Recovery rates from anemia were highest in the iron alone than the iron plus zinc group (74.8 vs. 62.9%;  $P < 0.048$ ). Zinc status however, was not improved and plasma zinc concentration was significantly decreased in both groups<sup>22</sup>.

Sprinkles were also tested for their efficacy in preventing anemia recurrence<sup>29,32</sup>. Four hundred and thirty-seven Ghanaian children 8-20 months old who had been treated for anemia and were non-anemic (Hb > 100g/L), were randomly assigned to either receive Sprinkles with iron alone (40 mg elemental iron), Sprinkles with iron and vitamin A (600 mg retinol equivalents) as retinol acetate,



iron(II) sulfate drops (40 mg/day), or a placebo sprinkles. Children were treated for 6 months and Hb, serum retinol and ferritin levels were assessed and then reassessed 12 months after supplementation ended. Non-anemic status was maintained in the majority of children (82.4%, 267/324) during the 6 month supplementation period. At 12 months, post-supplementation, mean Hb levels decreased equally within each intervention group. There were no significant differences in the proportion of children in each group that became anemic. Overall, anemia status was maintained by 77.1% (162/210) of the children.

Subsequent to this initial study involving the effect of Sprinkles on zinc status, Zlotkin et al., (2006) studied the effect of the interaction between Zn and iron combined in Sprinkles. Their study involved seventy-five 12 to 24 month old children with Hb  $\geq 7$ g/ L. Children were randomized to either a low Zn group (5 mg intrinsically labeled Zn gluconate) or high Zn group (10 mg of labeled Zn). Each of these groups also received 50 mg ascorbic acid (AA) and 30 mg of labeled Fe (ferrous fumarate). A third group received a control of no AA, 5mg standard food-grade Zn and 30 mg of labeled Fe. In each group the standard dose of 300 mg retinol equivalents of retinol acetate vitamin A were added to Sprinkles. There was no effect of Zn or AA on iron absorption and zinc in the form of Sprinkles were low in bioavailability. The percentage absorbed from either Zn treatment groups did not differ (low Zn 6.4%, high Zn 7.5%), but total Zn absorbed was significantly higher in the high Zn group (mean=.82mg) than the low Zn group (mean=0.31 mg)<sup>35</sup>.

The lowest efficacious does of Sprinkles was investigated by Hirve et al., in 2006<sup>36</sup>. Four hundred and thirty-two 6 to 18 month olds in Pune India were randomized to either receive 12.5, 20 or 30 mg of Sprinkles in the form of ferrous fumarate (FF), 20 mg of Sprinkles as micronized ferric pyrophosphate (MFP), 20 mg of ferrous glycine sulphate drops over a period of 2 months. Investigators

recommended a daily dose of 12.5 mg of Sprinkles FF as the preferable form in treating anemia in young children since they were as efficacious in increasing hemoglobin ( a mean increase of 15.0 g/l) and serum ferritin (a median increase of 2.0) as either drops or higher doses of Sprinkles. Further, compared to drops, there were fewer reported side-effects and better compliance with 12.5mg of Sprinkles as FF. These results were confirmed by Christofides et al., 2006 in a group of Ghanaian 6-18 month old anemic children<sup>37</sup>.

After these initial trials, efficacy of Sprinkles in anemia reduction as well as compliance and acceptability were demonstrated in different populations such as Canadian First nation and Inuit<sup>34</sup> Indonesian<sup>37</sup> and Cambodian<sup>38</sup> infants. Sprinkles were also found acceptable to mothers in Bangladesh<sup>26-27</sup>, China<sup>39</sup> and Ghana<sup>29</sup> and found to be as efficacious in improving anemia status as other iron containing infant supplements such as: Nutritabs and Nutributter<sup>27, 40</sup>.

Sprinkles effectively reduced treated and prevented anemia in large-scaled nutrition programs<sup>2</sup>. In Haiti, children between 9 and 24 months old received iron as Sprinkles in addition to a wheat-soy blend fortified food. These children had a mean Hb increase of 5.5g/L at the end of 2 months of a daily dosage of Sprinkles containing 12.5mg of iron compared to a control group that did not receive Sprinkles but had a mean decrease in Hb of 1 g/L<sup>2</sup>.

In addition to Haiti, Sprinkles has also been distributed as a part of other large-scale intervention programs such as in Mongolia<sup>3</sup>. However, little is known of the costs or effectiveness that may be associated with adopting this new intervention as compared to standard practices of iron supplementation. Even after demonstrating efficacy, interventions that efficiently target high-risk groups such as infants and young children should take into account: a) the cost of the intervention as well as the cost of identifying the high-risk groups; b) whether morbidity and mortality are

reduced among those that are targeted; c) related side effects that may be due to the identification of high risk groups or the intervention itself and d) the misclassification of individuals or communities<sup>41</sup>. Conducting a cost-effectiveness analysis takes into account factors a) through c).

#### *1.3.4 Defining Anemia in Infants and Young Children at High –Altitudes*

Approximately 140 million people, globally, live at altitudes above 2500 meters<sup>42</sup>. The majority of these high-altitude inhabitants live in the Andean regions of South America, or the mountain ranges of Asia and the Tibetan Plateaus. Indigenous human populations chronically exposed to high altitudes have characteristically high hemoglobin concentrations compared to sea-level residents<sup>43-46</sup>. At higher altitudes, these populations are exposed to life-long hypoxia due to reduced oxygen partial pressure in the atmosphere relative to sea-level. Exposure to atmospheres of low oxygen partial pressure creates a stress on the body's oxygen delivery system resulting in adaptations such as an increase in hemoglobin concentrations<sup>45-46</sup>.

High altitude induced hypoxic stress has been studied extensively by researchers from different scientific disciplines since the early 1900s<sup>47-48</sup>. For the majority, focus has been on acute and chronic responses to hypoxic stress, moving from descriptive accounts of the phenomena to obtaining a better understanding of the genetic bases of the differential adaptive responses of certain populations. Himalayan<sup>1</sup> and Andean<sup>2</sup> high-altitude natives have been the most studied population groups. Current knowledge is that, Tibetans (populations residing at the highest levels in the

---

<sup>1</sup> Tibetan Highlanders refer to individuals living proximal to the Asian mountain ranges and the Tibetan Plateaus. This region stretches across the of nations: Bhutan, China, India, Nepal, Tibet, Pakistan and Afghanistan.

<sup>2</sup> Andeans refer to those inhabitants residing in proximity to South America's longest and highest mountain range, the Andes Mountains with an average height of 4000m (13,000ft). The Andean states are the seven countries over which the mountains extend: Argentina, Bolivia, Chile, Colombia, Ecuador, Peru and Venezuela.

Himalayas and its environs) and Andean high-altitude natives have dissimilar hematological responses to high-altitude hypoxia<sup>44</sup>. In 1998, Beall and colleagues, after controlling for the confounding effects of iron deficiency, reported lower hemoglobin concentrations for Tibetan highlander relative to their Andean counterparts at similar altitudes<sup>48</sup>. This and other subsequent findings question the old model of a single universal response to life-long hypoxia<sup>43-47</sup>.

One area where there are major implications for this difference in hematological response of Andean and Tibetan highlander is in assessing the nutritional status of high-altitude residents; particularly with regards to the definition and identification of iron deficiency anemia. Anemia prevalence estimations and the identification of anemia are based on hemoglobin concentrations. When assessing iron deficiency anemia, above 1000m, the differences in hemoglobin levels of high-altitude populations, relative to sea-level residents becomes an integral part of public health interventions.

Several hemoglobin correction factors have been developed and utilized in population surveys to account for the differences in Hb levels of high-altitude residents, however, none have taken into account the differences between Andeans and Himalayan residents. In Dallman et al's, 1980 review of iron deficiency in infants and children, the authors suggested an approximate 4% correction factor for Hb for every 1000 meter elevation (this was based on adult data)<sup>49</sup>. However, Dirren et.al. 1994<sup>50</sup> noted that this factor was not aligned with the early observations Hurtado et. al. 1945<sup>51</sup> made regarding the non-linear relationship between altitude and hemoglobin. Consequently, this factor would underestimate anemia prevalence at high altitude and overestimate it at lower altitudes.

In 1994, Dirren et al. estimated hemoglobin corrections for 469 Ecuadorian children between the ages of 6 to 59 months living at altitudes ranging from sea-level

to 3400m. These children had normal iron status parameters<sup>50</sup>. The corrections were developed using an exponential (or logarithmic) regression of altitude on hemoglobin. This relationship was chosen based on the observed exponential decline of the partial pressure of oxygen with increasing altitude. A correction factor resulted:

$$\text{Hb} = 6.83 \times \exp(0.000445 \times \text{ALT}) + 113.3$$

Where Hb = hemoglobin concentration (g/L) and ALT= altitude in meters.

Dirren et al., (1994) concluded that the correction factor may also be applicable to other age groups and could either be applied to the then present world health organization cut-off for hemoglobin or subtracted from the hemoglobin measured at a particular altitude to obtain a sea-level value<sup>50</sup>.

In 1998, following Dirren et al's study, the center for disease control (CDC) published values for altitude-specific adjustment of Hb based on the CDC Pediatric Nutrition Surveillance System Based on hemoglobin levels of children 2-5 years old living between 1200 and 3000meters in the United States ( whether these children were iron-replete was not specified)<sup>52</sup>. The following equation was developed:

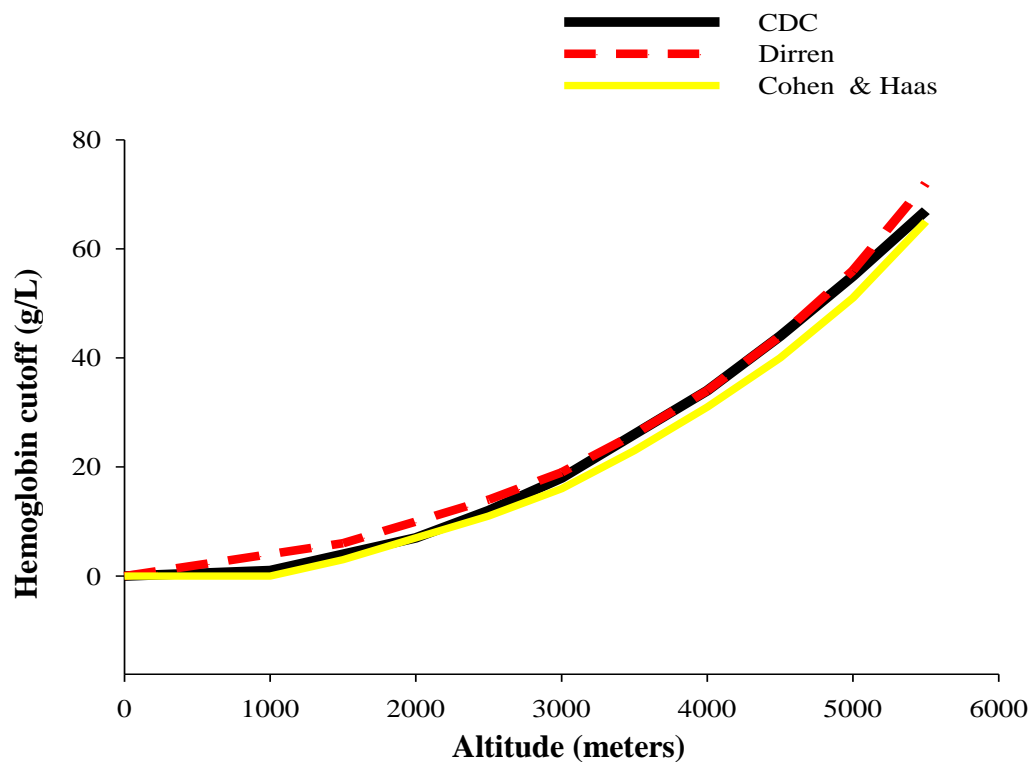
$$\text{Hb} = -0.32 \times (\text{altitude in meters}) \times 0.0033 + 0.22 \times (\text{altitude in meters} \times 0.0033)^2$$

Based on this equation, adjustments for altitude values were taken at 500m intervals above 1000m<sup>52-53</sup>. This equation results in Hb values 2 to 3 g/L lower, across a range of altitudes, than the corrections developed by Dirren et al. 1994. Speculations were that this was due to smaller sample size of the Ecuadorian study, and the assumption that the relationship between hemoglobin and altitude was exponential<sup>53</sup>.

In 1999, Cohen and Haas, using a nonlinear least squares Levenberg-Marquardt procedure, fit another exponential curve to the relationship between mean hemoglobin concentrations and altitude using non-anemic women residing in the United States (1000m), Ecuador (2800m) and Bolivia (3600 and 4800m)<sup>54</sup>. The following equation resulted:

$$\text{Hb} = 120 + 16.3 \times [\exp^{(0.00038 \times (\text{altitude} - 1000))}]$$

These authors compared their results to Dirren et al.'s curves for children and women of childbearing age and concluded that Dirren et al.'s anemia cut-off overestimated anemia prevalence by 50% in a sample 303 pregnant women living at 3600m and 4000m in Bolivia<sup>54</sup>. Cohen and Haas (1999) argue that Dirren et al.'s (1994) was not the best fitting curve for Hb and altitude data since it underestimated the slope of the relationship at higher altitudes (Figure 1.1).



**Figure 1.1:** Hemoglobin-altitude correction factor curves: Dirren et al., (1994)

To date, the majority of correction factors were developed from data based on Andean populations. Given the above mentioned differences between Andean and Himalayan physiological adaptations to altitude, a correction factor for the Andes may not be applicable to inhabitants of the Tibetan Plateaus and its environs. Given the current findings on the different physiological adaptations of Andeans and inhabitants of the mountainous regions of Asia <sup>45-46</sup> correction factors for hemoglobin should be developed that accommodate these differences<sup>55-56</sup>.

### *1.3.5 Anemia in the Central Asian*

Kyrgyzstan, Kazakhstan, Tajikistan, Turkmenistan, and Uzbekistan, collectively referred to as Central Asian Republics and Kazakhstan (CARK) were part of the Soviet Union before gaining independence in 1991. Beginning in the mid 1990s anemia was identified as a significant public health problem in the CARK. Results from the first nationally representative survey conducted by Demographic Health Surveys Measures (DHS) confirmed a high rate of anemia in three of these countries. Rates of anemia in children under 3 years old in Kazakhstan (1997), Uzbekistan (1996) and the Kyrgyz Republic (1997) were reported to be 69%, 61% and 50% respectively<sup>3</sup>. Potential causes of anemia cited by the DHS surveys were low consumption of meat products and a high consumption of tea by children 0 to 3 years of age. This survey motivated a UNICEF led integrated strategy (anemia prevention and control) to address the problem of iron deficiency anemia (IDA) through education, research, supplementation and fortification <sup>57-61</sup>.

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<sup>3</sup> Anemia was measured by assessing blood hemoglobin levels of children less 3 years of age .

### 1.3.6 Cost-effectiveness

Evaluating the cost-effectiveness of health interventions has been a priority for the world health organization (WHO) since 1990 and resulted in published guidelines to assist in conducting cost-effectiveness analysis (CEA) on various health interventions<sup>62</sup>. A CEA is presented as a means of assessing and improving health interventions. Very few analyses of the cost-effectiveness of iron supplementation or food fortification exist in the literature. The most notable is a study conducted by the WHO-CHOICE in 2004 that estimated the costs, effects and cost-effectiveness of iron fortification and iron supplementation for the control of iron deficiency in four global sub-regions (Africa, Asia, Europe, Latin-America)<sup>63</sup>. The researchers used a population model to simulate the health of a population over time. Assuming a 95% coverage rate, authors concluded that iron supplementation had more of an impact on overall health, averting approximately 2.5 million disability adjusted years (DALYs) more than iron fortification, in regions where rates of child and adult mortality were high<sup>63</sup>. Iron supplementation was deemed feasible and efficacious in all regions.

***These findings, however, were based on pregnant women and not on children 6 to 24 months old who are the most vulnerable group.*** Further, the authors encouraged the adaptation of CEA techniques to conduct location-specific analyses to help inform appropriate decision making. Although this investigation provided an indication of the cost-effectiveness of iron supplementation and fortification, ***there is still a need to do a community-based evaluation of the cost-effectiveness of iron supplementation for anemia control.*** In these times of limited resources, program funders, planners, and managers need to know which strategies are most effective from both a programmatic and financial perspective.

Recommendations for addressing the problem of IDA in infants and children are to adapt a multi-factorial approach. In resource-poor nations, choosing among



available methods will depend on the relative cost-effectiveness of each strategy. However, *there is a lack of knowledge regarding the cost-effectiveness of iron interventions in infants and young children*. Evaluating the cost-effectiveness will not only provide a means of assessing the efficiency of an innovative intervention on anemia but also help decision makers to improve the direction in which iron supplementation programs are leading so that resources can be transferred to the most efficient programs.

#### ***1.4. Objective***

With the overall objective of contributing to the elucidation of the problem of anemia in the Central Asian Republics and Kazakhstan, this dissertation focuses on the country where anemia prevention and control strategies have had the least impact among pre-school children: Kyrgyzstan. Specific objectives of each study are to further clarify how anemia is defined in Central Asia, to understand the risk factors for anemia in preschool children in Kyrgyzstan and to estimate costs, effects and cost-effectiveness of the use of a home-based method of iron fortification in treating and preventing anemia in pre-school children in Kyrgyzstan. Our findings will be of interest to policy makers as well as program managers and hopefully will help guide their work to reduce and prevent anemia in preschool children in Kyrgyzstan and other Central Asian countries.

## REFERENCES

1. Kraemer K, Zimmermann M. ed. Nutritional Anemia. Basel, Switzerland: Sight and Life Press, 2007.
2. Menon P, Ruel MT, Loechl CU, et al. Micronutrient Sprinkles reduce anemia among 9- to 24-mo-old children when delivered through an integrated health and nutrition program in rural Haiti. *J Nutr* 2007; 137:1023-30.
3. World-Vision. Effectiveness of Home-based fortification with sprinkles in an Integrated Nutrition Program to address rickets and anemia. Ulaanbaatar, 2005.
4. Gillespie S, Kevany J, Mason J. Controlling iron deficiency: a report based on an ACC/SCN workshop Geneva, Switzerland United Nations, Administrative Committee on Coordination/Subcommittee on Nutrition, 1991.
5. Stoltzfus R, and Dryefuss, ML. Guidelines for the use of iron supplements to prevent and treat iron deficiency anaemia. Washington DC: ISLI Press, 1998.
6. Stoltzfus R, Dryefuss M. Iron deficiency: Global prevalence and consequences. *Food and Nutrition Bulletin* 2003; 24:S99-S103.
7. WHO/UNICEF/UNU. Iron deficiency anaemia: assessment, prevention and control. Geneva: World Health Organization, 2001.
8. Schlutink W, Gross R. Iron Deficiency alleviation in developing countries. *Nutr Res Rev* 1996; 9:281-293.
9. Lutter C, Rivera J. Nutritional status of infants and young children and characteristics of their diets. *J Nutr* 2003; 133:2941S-9S.
10. Lutter C, Dewey K. Proposed nutrient composition for fortified complementary foods. *J Nutr* 2003; 133:3011S-20S.
11. Gibson R, Ferguson E, Lehrfeld J. Complementary foods for infant feeding in developing countries: their nutrient adequacy and improvement. *Eur J Clin Nutr* 1998; 52:764-70.

12. Bell JG, Keen CL, Lönnerdal B. Effect of infant cereals on zinc and copper absorption during weaning. *Am J Dis Child* 1987; 141:1128-32.
13. Trowbridge T. Prevention and control of iron deficiency: Priorities and action steps. *J Nutr* 2002; 132:880S-882S.
14. Yip R. Prevention and control of iron deficiency in developing countries. *J Nutr* 2002; 132:802S-5S.
15. Yip R. Iron supplementation: country level experiences and lessons learned. *J Nutr* 2002; 132:859S-61S.
16. Mora J. Iron supplementation: overcoming technical and practical barriers. *J Nutr* 2002; 132(4) Suppl: 853S-5S.
17. Chitpan M, Chavasit V, Kongkachuichai R. Development of fortified dried broken rice as a complementary food. *Food Nutr Bull* 2005; 26:376-84.
18. Hurrell R, Lynch S, Bothwell T, et al. Enhancing the absorption of fortification iron. A SUSTAIN Task Force report. *Int J Vitam Nutr Res* 2004; 74:387-401.
19. Allen L, Gillespie S. What Works? A Review of the efficacy and effectiveness of nutrition interventions. Manila, Philippines: United Nations Administrative Committee on Coordination Sub-Committee on Nutrition (ACC/SCN) in collaboration with the Asian Development Bank (ADB), 2001.
20. Micronutrient-Initiative. Anemia prevention and control: What works? : Micronutrient Initiative, 2003.
21. Yip R. The challenge of improving iron nutrition: limitations and potentials of major intervention approaches. *Eur J Clin Nutr* 1997; 51 S16-24.
22. Zlotkin S, Antwi K, Schauer C, GA Y. Home-fortification with iron and zinc sprinkles or iron Sprinkles alone successfully treats anemia in infants and young children. *J Nutr* 2003;133:1075-80.

23. Zlotkin SH, Schauer C, Christofides A, Sharieff W, Tondeur M, SM H. Micronutrient Sprinkles to control childhood anaemia. 2005.
24. Zlotkin S, Christofides A, Hyder S, Schauer C, Tondeur M, W S. Controlling iron deficiency anemia through the use of home-fortified complementary foods. *Ind J of Ped* 2004; 71:1015-9.
25. Liyanage C, Zlotkin S. Bioavailability of iron from micro-encapsulated iron Sprinkle supplement. *Food Nutr Bull* 2002;23:133-7.
26. Ziauddin Hyder SM, Haseen F, Rahman M, Zlotkin SH. Delivery of microencapsulated iron sprinkles in rural poor through female health workers: lessons learned at BRAC in Bangladesh. Canadian International Health Conference. Ottawa, Canada, 2004.
27. Adu-Afarwuah S, Lartey A, Brown KH, Zlotkin S, Briend A, Dewey KG. Home fortification of complementary foods with micronutrient supplements is well accepted and has positive effects on infant iron status in Ghana. *Am J Clin Nutr* 2008;87:929-38.
28. Ziauddin Hyder S, Haseen F, Rahman M, Zeng L, Zlotkin SH. Efficacy of daily vs weekly home fortification of weaning foods with Sprinkles among infants and young children in Bangladesh. International Nutritional Anemia Consultative Group (INACG). Lima, Peru, 2004.
29. Zlotkin S, Arthur P, Antwi K, Yeung G. Treatment of anemia with microencapsulated ferrous fumarate plus ascorbic acid supplied as Sprinkles to complementary (weaning) foods. *Am J Clin Nutr* 2001;74:791-5.
30. Zlotkin S. Current issues for the prevention and treatment of iron deficiency anemia. *Indian Pediatr* 2002;39 125-9.
31. Ip H, Hyder SM, Haseen F, Rahman M, Zlotkin SH. Improved adherence and anaemia cure rates with flexible administration of micronutrient Sprinkles: a new public health approach to anaemia control. *Eur J Clin Nutr*. 2007 Sep 26.
32. Zlotkin S, Antwi K, Schauer C, Yeung G. Use of microencapsulated iron(II) fumarate sprinkles to prevent recurrence of anaemia in infants and young children at high risk. *Bull World Health Org* 2003;81:108-15.

33. Baltussen R, Knai C, Sharan M. Iron fortification and iron supplementation are cost-effective interventions to reduce iron deficiency in four subregions of the world J Nutr 2004;134.
34. Christofides A, Schauer C, Sharieff W, Zlotkin SH. Acceptability of micronutrient sprinkles: a new food-based approach for delivering iron to First Nations and Inuit children in Northern Canada. Chronic Dis Can 2005;26:114-20.
35. Zlotkin SH, Schauer C, Owusu Agyei S, et al. Demonstrating zinc and iron bioavailability from intrinsically labeled microencapsulated ferrous fumarate and zinc gluconate Sprinkles in young children. J Nutr 2006; 136:920-5.
36. Hirve S, Bhawe S, Bavdekar A, et al. Low dose 'Sprinkles'-- an innovative approach to treat iron deficiency anemia in infants and young children. Indian Pediatr 2007;44:91-100.
37. Christofides A, Asante KP, Schauer C, Sharieff W, Owusu-Agyei S, Zlotkin S. Multi-micronutrient Sprinkles including a low dose of iron provided as microencapsulated ferrous fumarate improves haematologic indices in anaemic children: a randomized clinical trial. Matern Child Nutr 2006;2:169-80.
38. Giovannini M, Sala D, Uselli M, Livio L, Francescato G, Braga M, Radaelli G, Riva E. Double-blind, placebo-controlled trial comparing effects of supplementation with two different combinations of micronutrients delivered as Sprinkles on growth, anemia, and iron deficiency in Cambodian infants. J Pediatr Gastroenterol Nutr 2006;42:306-12.
39. Yeung D, Yap J, Cheng C. Consumer acceptance of a home food iron fortificant. International Nutritional Anemia Consultative Group (INACG). Lima, Peru, 2004.
40. Tondeur MC, Schauer CS, Christofides AL, Asante KP, Newton S, Serfass RE, Zlotkin SH. Determination of iron absorption from intrinsically labeled microencapsulated ferrous fumarate (sprinkles) in infants with different iron and hematologic status by using a dual-stable-isotope method. Am J Clin Nutr 2004; 80:1436-44.
41. Loevinsohn B, Sutter R, Costales M. Using cost-effectiveness analysis to evaluate targeting strategies: the case of vitamin A supplementation. Health Policy Plan 1997; 12:29-37.

42. Frisancho AR. Human Adaptation to High-Altitude Environments. In: Anonymous humankind evolving: an exploration of the origins of human diversity. Dubuque, Iowa: Kendall/Hunt, 2006:301.
43. Ballew C, Garruto RM, Haas JD. High-Altitude hematology: paradigm or enigma? In: Little MA, Haas JD., ed. Human population biology : a transdisciplinary science. New York : Oxford University Press, 1989:338.
44. Beall CM. Two routes to functional adaptation: Tibetan and Andean high-altitude natives. *Proc Nat Acad Sci USA* 2007;104 Suppl 1:8655-60.
45. Beall CM. Adaptations to altitude: A current assessment. *Annu Rev Anthropol* 2001;30: 423-56.
46. Beall CM, Reichsman AB. Hemoglobin levels in a Himalayan high altitude population. *Am J of Phys Anthropol* 1984;63:301-6.
47. Beall CM, Goldstein MC. Hemoglobin concentration of pastoral nomads permanently resident at 4,850-5,450 meters in Tibet. *Am J Phys Anthropol* 1987; 73:433-8.
48. Beall CM, Brittenham GM, Strohl KP, et al. Hemoglobin concentration of high-altitude Tibetans and Bolivian Aymara. *Am J Phys Anthropol* 1998; 106:385-400.
49. Dallman PR, Siimes MA, Stekel A. Iron deficiency in infancy and childhood. *Am J of Clin Nutr* 1980; 33:86-118.
50. Dirren H, Logman MH, Barclay DV, Freire WB. Altitude correction for hemoglobin. *Eur J Clin Nutr* 1994; 48:625-32.
51. Hurtado A, Merino C, Delgado E. Influence of anoxemia on hemopoietic activity. *Arch Int Med* 1945; 75:284-323.
52. Yip R. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control* 1998;47:1-29.

53. Nestel, Penelope. "Adjusting hemoglobin values in program surveys." International Nutritional Anemia Consultative Group. June 2002.
54. Cohen JH, Haas JD. Hemoglobin correction factors for estimating the prevalence of iron deficiency anemia in pregnant women residing at high altitudes in Bolivia. *Pan Am J Pub Hlth* 1999;6:392-9.
55. Dang S, Yan H, Yamamoto S, Wang X, Zeng L. Poor nutritional status of younger Tibetan children living at high altitudes. *Eur J Clin Nutr* 2004; 58:938-46.
56. Kolsteren P, Atkinson S, Maskall K. Une enquête nutritionnelle au Tibet. *Santé Montrouge, France* 1995; 5:247-52.
57. Sharmanov A. Anaemia in Central Asia: demographic and health survey experience. *Food and Nutr Bull* 1998;19:307-17.
58. Darnton-Hill I. Anaemia prevention and control mid-term evaluation for UNICEF-CARK regional office Central Asia Republics and Kazakhstan. New York: Human Nutrition Institute, Columbia University, 2002.
59. Gleason GR, Sharmanov T. Anemia prevention and control in four Central Asian Republics and Kazakhstan. *J Nutr* 2002;132:867S-870S.
60. Anonymous. Kyrgyz Republic 1997: results from the Demographic and Health Survey. *Stud Fam Plann* 1999; 30:347-51.
61. Scrimshaw N. Frequency, cause and significance of iron deficiency for the children of Central Asia. *J Child Health* 1998; 9:47.
62. Tan Torres T, Baltussen RM, Adam T, Hutubessy RC, Acharya A, Evans DB. WHO Guide to Cost-Effectiveness Analysis. World Health Organization Geneva, Switzerland, 2003.
63. Baltussen R, Knai C, Sharan M. Iron fortification and iron supplementation are cost-effective interventions to reduce iron deficiency in four subregions of the world. *J Nutr* 2004;134:2678-84.

64. Baker SJ, DeMaeyer EM. Nutritional anemia: its understanding and control with special reference to the work of the World Health Organization. *Am J Clin Nutr* 1979; 32:368-417.



## CHAPTER 2

### DEFINING ANEMIA IN ASIAN HIGH-ALTITUDE POPULATIONS

#### ***2.1 INTRODUCTION***

For nearly half a century anemia has had a major impact on global public health both due to its high prevalence and its associated morbidities<sup>1,2</sup>. Anemia affects approximately 2 billion people worldwide most of whom are women and children residing in developing countries. Anemic women and children are at increased risk of morbidity and mortality and experience reduced intellectual and work capacities<sup>1</sup>. Given the global prevalence of anemia and its impact on the health of women and children, the prevention and control of anemia continues to be the focus of many public health interventions worldwide.

A necessary first step in the control and prevention of anemia is establishing the population prevalence of anemia<sup>2</sup>. The most common approach worldwide is to use a cut-off, set below the 95<sup>th</sup> percentile of the nonanemic population. Individuals with hemoglobin concentrations falling below this cut-off are classified as anemic. Hemoglobin (Hb) values can be affected by many factors such as altitude. In population-based surveys of high-altitude residents, individual hemoglobin values must be adjusted for altitude before classifying individuals as anemic and establishing prevalence.

The effect of altitude on hemoglobin levels is a critical factor that must be taken into account when defining anemia. Approximately 140 million people, globally, live at altitudes above 2500 meters<sup>3</sup>. These high-altitude inhabitants, living in the Andean regions of South America, or the Asian mountain ranges and the Tibetan Plateau, experience a lifelong hypobaric hypoxic environment that results in human physiological and morphological adaptive responses<sup>3,4,5</sup>. Among the most noted of which is an elevated hemoglobin concentration relative to sea-level inhabitants<sup>3,4,5</sup>.

The initial investigations of human adaptation to high-altitude hypoxia were mostly conducted in the Andes<sup>4-9</sup>. These studies greatly influenced the concretization and acceptance of the concept of a universal human hematological response to lifelong hypoxia, beginning at altitudes as low as 1600m<sup>5, 6, 8, 10</sup>. However, some researchers questioned whether the Andean response to altitude was universal and began to examine the hemoglobin response to chronic hypobaric hypoxia of indigenous populations of the Himalayas and the Tibetan Plateau<sup>14-16</sup>. After adjusting for the confounding effect of iron-deficiency that could affect hemoglobin synthesis, Beall et al. (1998), found Tibetans had a blunted hemoglobin response to altitude compared to the Andeans<sup>16</sup>. Hemoglobin concentrations for both Tibetan men and women were, on average, 36g/L lower than Andean residents at the same altitude and were only slightly elevated from sea-level reference values<sup>14-19</sup>.

When assessing anemia in these populations, adjustments have to be made to accommodate differences in Hb concentrations relative to sea-level residents. Altitude-based hemoglobin correction factors were developed based on findings in the Andes and are currently used worldwide<sup>4,8,11-13</sup>. However, given the findings and understandings of the different physiological adaptations between Andeans and high-altitude residents in Asia, correction factors should be developed that incorporate these differences.

In this research, we develop altitude correction factors for hemoglobin that capture how hemoglobin concentrations vary in Asian lifelong residents at high altitude. The definition of a correction factor requires the identification of normative hemoglobin concentrations. Data availability of normative hemoglobin values of this population group is limited. Therefore, in this study, we used mixed distribution analysis to identify the parameters of the hemoglobin distributions of non-anemics in sample distributions containing admixtures of both anemic and non-anemic

individuals. Concerns with polycythemia and thalassemia were not considered since they have not been found to be highly prevalent in Asian populations that historically reside at high altitudes <sup>6,15</sup>. Using nationally representative data on hemoglobin collected in several countries situated in the mountainous regions of Asia, we modeled how hemoglobin concentrations, in non-anemic samples, varied with altitude, in high-altitude Asian residents experiencing chronic hypobaric hypoxic stress. The end goal was to model how hemoglobin changes with altitude in Asian populations and use this derived relationship to develop altitude adjustments for hemoglobin levels that can be used in Asia. Based on earlier findings in the literature we expect our correction factors to result in more moderate corrections in hemoglobin levels as altitude increases. The use of our new adjustments would avoid the potential overestimation of anemia prevalence that can occur with Andean-based correction of Asian hemoglobin levels.

## **2.2 METHODS**

### **2.2.1 Data**

Demographic and Health Survey (DHS) data from several countries in Asia were used for this analysis (Table 2.1). The USAID<sup>4</sup> funded MEASURE<sup>5</sup> DHS program conducts worldwide population-based surveys collected from large and nationally-representative samples in a standardized manner. The DHS database was searched and countries included in this analysis were those from Asia for which access was permitted, and that had all the following variables: unadjusted Hb, altitude and age. DHS assessment of hemoglobin concentration is standardized across all of its surveys using a Hemocue to test the blood samples obtained through a finger prick for

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<sup>4</sup> United States Agency for International Development

<sup>5</sup> Monitoring and Evaluation to Assess and Use Results

women and a heel prick for young children<sup>20</sup>. Testing was conducted by medically trained personnel.

**Table 2.1:** Data Characteristics

Country	Year	Women (n)	% anemia	Children (n)	% anemia	Altitude (m)
Armenia	2005	6080	25	1106	37	695-2834
Armenia	2000	6137	12	1334	24	420-2230
India	1998/99	79663	52	20016	74	0-3875
Kyrgyzstan	1997/98	3767	38	1021	50	420-2380
Nepal	2006	10646	36	4692	48	51-3212

(n) = Total sample size, (m) = meters, %= percentage

### 2.2.2 Data Analysis

#### Mixed Distributional Analysis

Mixed distributional analysis (MDA)<sup>6</sup>, a method employed in various fields to identify mixtures of statistical distributions in populations<sup>21-25</sup>, has also been used to distinguish the anemic and non-anemic proportions of a sample of hemoglobin concentrations taken from a population with an admixture of both anemic and non-anemic proportions<sup>6,9,24</sup>. Samples drawn from heterogeneous populations contain a composite of statistical distributions which are comprised of simpler distributions<sup>21</sup>. These distributions reflect the different probability density functions of the mixed population<sup>25</sup>. In this analysis we used MDA to identify the non-anemic sub-groups in each of our populations at different altitude ranges.

Hemoglobin distributions can be defined in terms of identifiable sub-populations; anemic and non-anemic<sup>26,27</sup>. There is an overlap between these two distributions with the anemic distribution down-shifted relative to the non-anemic distribution<sup>26,27</sup>. Often the data are not available for the individual distributions and

<sup>6</sup> When the number of components present are finite then this is referred to as finite mixture distribution analysis

mixed distribution analysis can be used as a model to estimate the parameters of each component of the mixture. In the case of this analysis, MDA was used to estimate the following parameters: mean( $\mu$ ), standard deviation ( $\sigma$ ) and the proportion of the sample ( $\pi$ ) for each component of the mixture.

Different methods of mixed distribution analysis have been employed; in this study, the maximum likelihood method was used. Earlier work using mixed distribution analysis to identify sub-populations in a distribution of Hb (for the purpose of estimating anemia prevalence) used probability plotting<sup>24,28</sup>. These studies were useful in confirming the validity of the assumptions made regarding the distribution of hemoglobin values. The first assumption is that the anemic and non-anemic distributions are different. The second is that only the latter of the two distributions is Gaussian and the shape of the anemic distribution is unspecified. In addition, these studies validated the use of mixed distribution analysis as a tool for defining anemia yet emphasized that probability plotting was not appropriate when prevalence of anemia was greater than 5%. At a higher prevalence, maximum likelihood estimation, a method that employs an iterative procedure, was more appropriate<sup>24</sup>.

In 1985, Tufts et al. used both probability plotting and the maximum likelihood procedure to estimate population parameters and found results from both methods to be comparable<sup>6</sup>. The researchers emphasized the need for adequate sample sizes when estimating parameters using maximum likelihood estimate techniques. Haas and Cohen (1999) later compared the maximum likelihood estimate of mixed distribution analysis to a three-criterion<sup>7</sup> model of iron deficiency to estimate the prevalence of

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<sup>7</sup> The three criteria model of iron-deficiency involved the assessment of iron status using serum ferritin, transferrin saturation and erythrocyte protoporphyrin

IDA in Costa Rican children and found mixed distribution analysis to be an accurate estimate of the prevalence of IDA given sufficient sample size<sup>9</sup>.

### Maximum Likelihood Estimate

The maximum likelihood estimate method was used in this study to estimate parameters underlying the Hb probability distributions for a set of data. During maximum likelihood estimation values are found of the unknown set of parameters that are “most likely” to have been generated given the data at hand relative to other values. This method is ideal for large samples and provides consistent estimates that are asymptotically normally distributed, minimum in variance, and unbiased<sup>21</sup>.

To obtain the maximum likelihood estimate, calculus is used to find the maximum point of the likelihood function:  $L(\Psi; x) = \prod_{j=1}^n f(x_j | \Psi)$  where,  $X$  is a continuous random variable with a probability density function (pdf)  $f(x | \Psi)$ , where  $\Psi = (\Psi_1, \dots, \Psi_d)^T$  is the parameter vector that is to be estimated from randomly sampled independent observations  $x_1, \dots, x_n$  (sample of size  $n$ ). Traditionally, differentiation is used to find the particular  $\Psi$  that maximizes the likelihood function,  $L$ , with respect to the other components. In this case of maximum likelihood estimation, an iterative (using successive approximations to the solution starting from an initial guess) technique is used to maximize the logarithm of  $L$ .

The software used to fit mixtures of distributions was a form of the program MIX that was present as library package *mixdist* for the cross-platform open-code R environment.

Decisions regarding the best model that fit the data were based on a combination of the following factors for each run of the analysis:

- 1) Rmix provided a goodness-of-fit chi-square test ( $\chi^2$ ), printed after each fitting step, which indicated how well the mixture distribution fit the histogram of Hb

(Figure 2.1). This tested the null hypothesis that more than one distribution was present and a non-significant p-value ( $p > .05$ ) was interpreted as a good fit and the null hypothesis was not rejected.

- 2) The degree of freedom (df) of the chi-square test was equal to the number of grouping intervals, minus 1, minus the number of parameters estimated. Parameters that were held fixed were not included in the estimation of the df. Results with only  $df > 9$  were considered adequate (personal communication Peter Macdonald, 2007) regardless of the  $\chi^2$  results.
  - 3) Estimated parameters were considered for their biological plausibility. Results with different estimates were compared based on the proportions (“pi” in Figure 2.1) of the sample that fell in the non-anemic distribution. Proportions that seemed feasible based on the initial percentages of anemia present in the sample were considered valid.
  - 4) Graphical results presented at the beginning and end of each estimation attempt were also viewed to determine whether or not the fit was adequate (Figure 2.1).
- For each country and altitude level, several models were run with different constraints on the parameters to see which model would best fit the data from a biological perspective. Hb distributions often have mean and standard deviations ( $\sigma$ ) that differ for the anemic and non-anemic distributions<sup>26</sup>. Based on the recommendations of Yip et al., (1996) assessment of normal distributions, a standard deviation of 10g/L was used for the non-anemic. Models had the following characteristics: no constraints on any of the parameters, setting all  $\sigma$ s equal, setting the  $\sigma$  for the non-anemic distribution to 10g/L and letting the anemic distribution vary unconstrained. Further, based on the initial frequency distributions, attempts were made to identify two and three distributions.

The most consistent results were obtained with the restriction of the non-anemic distribution and a non-restricted anemic distribution.

Parameters\*:  

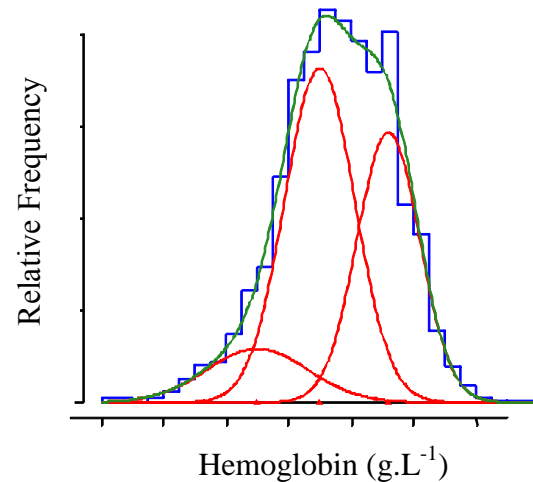
pi	mu	sigma
1	0.1190	70.0 16.12
2	0.5125	90.0 11.22
3	0.3685	112.0 10.00

Standard Errors:  

pi.se	mu.se	sigma.se
1	0.02196	NA 1.569
2	0.04711	NA 1.017
3	0.02963	0.6824 NA

Analysis of Variance Table  

	Df	Chisq	Pr (>Chisq)
Residuals	20	27.554	0.1204



\* Pi= proportion of total sample assigned to each of the subgroups identified, mu= meanHb (g/l) for each subgroup identified, sigma=standard deviation for each sub-group identified. NA= not Available and appear where standard errors are not estimated for each parameter. Df= degrees of freedom, Pr= probability, Chisq = Chi square

**Figure 2.1:** Example of mixed distribution analysis: Three-distribution fit

A 3 distribution fit was decided to be the best fit (Figure 2.1). The distribution to the farthest right in Figure 2.1 was considered to be the non-anemic distribution. To test our samples for the presence of polycythemia, a disorder characterized by increased red blood cell mass, that may have affected the estimated mean and standard deviations, we constructed cumulative probability plots of sub-samples of our data (data not shown) and used Tufts et al.'s (1985) cut-off for the presence of polycythemia of less than 22 g/L. We found no polycythemia present at the higher end of our distribution of hemoglobin values<sup>6</sup>. Since less is known about anemic distributions<sup>6,26</sup> the other two distributions were grouped together and defined as anemic based on the proportions (pi) defined during analysis the mixed distribution fit.



### ***2.2.3 Data Preparation***

DHS unadjusted hemoglobin values of non-pregnant, non-lactating, non-smoking women of childbearing age and children 6 to 59 months, were used for this analysis; women who were pregnant within the year of the survey, currently pregnant at the time of the survey, or breastfeeding were dropped from the sample. Some datasets contained extreme Hb values (such as 0); analysis was done both with and without these values and after discussions with DHS staff these values were deemed erroneous and dropped.

For each country, data were stratified according to altitude ranges: less than 1000 meters, 1000-2000 meters and greater than 2000 meters. In the case of countries with large sample sizes, such as India, another group was defined above 3000 meters. The mean altitude was calculated for each range. At each altitude range, a mean hemoglobin value for non-anemic cases was estimated using mixed distributional analysis.

This process was repeated for each country and for women and then children. The mean hemoglobin values of non-anemic persons were modeled as a function of the change in the pooled mean altitudes values for women and children. Using an exponential function of the form:  $y = a \cdot \exp^x + c$ <sup>8</sup>, the best curve that fit the set of data was found for women and children.

Analysis and data preparation were done using SPSS 15, Microsoft Excel, and SAS 9 ( for final model predictions) and Sigma Plot 10.0 (for the production of graphs). The program MIX 2.3<sup>9</sup>, run on the R 2.4.0 platform was used to perform maximum likelihood estimates of mixed distribution analysis on the sample of hemoglobin values.

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<sup>8</sup> Where a, b and c are constants calculated in the regression.

<sup>9</sup> MIX was developed by Professor Peter Macdonald at McMaster University

## **2.3 RESULTS**

### *2.3.1 Country Characteristics*

Details of characteristics of the samples included in this analysis are shown for women and children (Table 2.2). The sample sizes varied across countries for non-pregnant, non-lactating women ranging from 382 in Kyrgyzstan to 17879 for India. Similarly, sample sizes for children were lowest in Kyrgyzstan (822) and highest in India (6392). Mean hemoglobin, for women, were significantly different across all countries ( $p < .001$ ). The lowest mean was  $120.3 \pm 19.3$  g/L for India and the highest was  $137.2 \pm 14.7$  for Armenia 2001. For children mean hemoglobin values followed a similar pattern with Kyrgyzstan and India having the lowest mean hemoglobin levels ( $111.4 \pm 16.5$  g/L and  $99.5 \pm 19.6$  g/L respectively) and the two Armenian samples the highest ( $118.4 \pm 16.34$  g/L and  $121.8 \pm 14.6$  g/L).

The samples of children in Kyrgyzstan and India had similar mean ages ( $20 \pm 9$  months) which were both lower than Nepal ( $30 \pm 17$  months) and both Armenian samples ( $32 \pm 15$  and  $34 \pm 16$  months). Average ages for women ranged from 28 years in Kyrgyzstan to 34 years in India.

### *2.3.2 Mixed Distribution Analysis*

Mixed distribution analysis was used to estimate the mean, standard deviation and sample proportion of the non-anemic and anemic distribution at each altitude level for each country (Table 2.3). Mean altitude varied from 255 meters in Nepal to 3399 meters in India. India had the highest proportions of anemic (65-83%) and Armenia 2000 the lowest (12-65 %). Exceptions were women and children living above 2000m in Armenia.

Mean hemoglobin concentrations were lower for anemic than for non-anemic distributions for every country (Table 2.3).

**Table 2.2 : Sample Characteristics**

Country	Year	Mean Hb (SD)	n	Mean Altitude (m)	Mean Age (y)
<b><i>Non-pregnant, Non-lactating women</i></b>					
Armenia	2005	132.2(18.3)	5671	1368 (435)	32(11)
Armenia	2001	137.2 (14.7)	5630	1296 (399)	32(10)
India	1998/1999	120.3(19.3)	17879	776 (698)	34 (8)
Kyrgyzstan	1997	123.3 (19.4)	382	1287 (566)	28 (5)
Nepal	2006	127.3(16.5)	7013	784 (724)	30(11)
<b><i>Children 6-59 months</i></b>				<b>Mean Age (m)</b>	
		118.4			
Armenia	2005	(16.34)	1024	1343(444)	32(15)
Armenia	2001	121.8(14.6)	1370	1316(431)	34(16)
India	1998/1999	99.5(19.6)	6392	773(666)	20(9)
Kyrgyzstan	1997	111.4(16.5)	822	1320(559)	20(9)
Nepal	2006	111.7(16.8)	4692	809(741)	30(17)

Hb =hemoglobin, (n)= sample size, SD= (standard deviation), (m)= meters, (y)= years

### 2.3.3 Hemoglobin Altitude Curves

Based on the values presented in Table 2.3, a relationship between mean altitude and mean hemoglobin values of non-anemics was defined. Using a Marquardt-Levenberg algorithm, an exponential curve of the form:

$$\text{Hemoglobin (g/L)} = a * \exp^{b * \text{altitude}} + c,$$

where a, b and c are constants calculated in the regression, was used to fit the relationship between mean hemoglobin for non-anemic sub-populations at corresponding mean altitudes for the pooled data for women and children from all countries. This exponential curve was previously used by Dirren et al. (1994), and Cohen and Haas (1999) in developing their Andean-based correction factors<sup>8,12</sup>.

Dirren et al.'s, (1994) correction factor was based on the equation:

$$\text{Hemoglobin (g/L)} = 6.83 \times \exp^{0.000445 \times \text{altitude}} + 113.3.$$

Similarly the correction factors Cohen and Haas (1999) used were based on:

$$\text{Hemoglobin (g/L)} = 120 + 16.3 \times [\exp^{(0.00038 \times (\text{altitude} - 1000))}].$$

**Table 2.3:** Estimated Parameters

Country	Subjects	Mean Altitude (m)	Anemic			Non-Anemic		
			pi	Mean	SD	pi	Mean	SD
Armenia 2000	Women	885	12	125	25	88	137	10
		1462	12	125	25	88	141	10
		2123	65	125	25	35	147	10
	Children	879	46	110	17	55	121	10
		1484	53	117	17	47	127	10
		2128	53	113	21	47	131	10
Armenia 2005	Women	897	27	123	20	73	134	10
		1407	30	124	16	70	138	10
		2138	61	125	26	39	141	10
	Children	892	54	109	14	46	124	10
		1404	55	115	18	44	126	10
		2123	60	102	14	40	131	10
India 1998/1999	Women	410	79	105	11	19	132	10
		1464	80	115	17	20	139	10
		2263	73	115	17	27	139	10
		3399	75	122	12	25	144	10
	Children	380	65	97	7	3	116	10
		1433	68	100	8	32	123	10
		2591	83	105	15	17	132	10
Nepal	Women	255	77	115	18	23	129	10
		1409	80	113	17	20	133	10
		2168	40	117	14	16	149	10
		2882	70	133	14	30	154	10
	Children	242	43	105	10	57	115	10
		1439	43	118	11	57	123	10
		2176	56	115	11	44	129	10
Kyrgyzstan	Women	2933	65	103	9	35	132	10
		752	43	105	24	57	129	10
		1463	58	115	17	42	132	10
	Children	2133	47	125	15	53	139	10
		765	64	103	18	36	116	10
		1441	77	103	15	23	122	10
		2146	86	110	12	14	133	10

(m)=meters, SD= standard deviation, % = percent, Pi= proportion of total sample assigned to the subgroup identified

**Table 2.4** : Mean hemoglobin values for non-anemic sea-level and high-altitude natives

Source	Country	Hb (g/L)	Mean Altitude (m)
<b>Women</b>			
Beall 1984	Nepal	146.0	3405
Beall 1987	Tibet, Nepal	167.0	5150
NHANES III	USA	135.0	0
<b>Children</b>			
NHANES III	USA	123.2	0

(g/L)= grams per liters, m= meters, Hb= Mean Hemoglobin

Citing the lack of biological or statistical evidence for a relationship between hemoglobin and altitude below 1000 meters, the latter group of researchers truncated their data below 1000 meters. In this study, normative hemoglobin values for both healthy non-anemic women and children at sea-level were used to anchor each curve<sup>10</sup>. In addition, the range of data in this analysis was extended for the women's curve by an addition of mean hemoglobin values of non-anemic, non-pregnant, non-lactating female high-altitude natives of childbearing age published in the literature<sup>14, 15</sup>(Table 2.4).

The following are best fit curves for children and non-pregnant, non-lactating women estimated in this study.

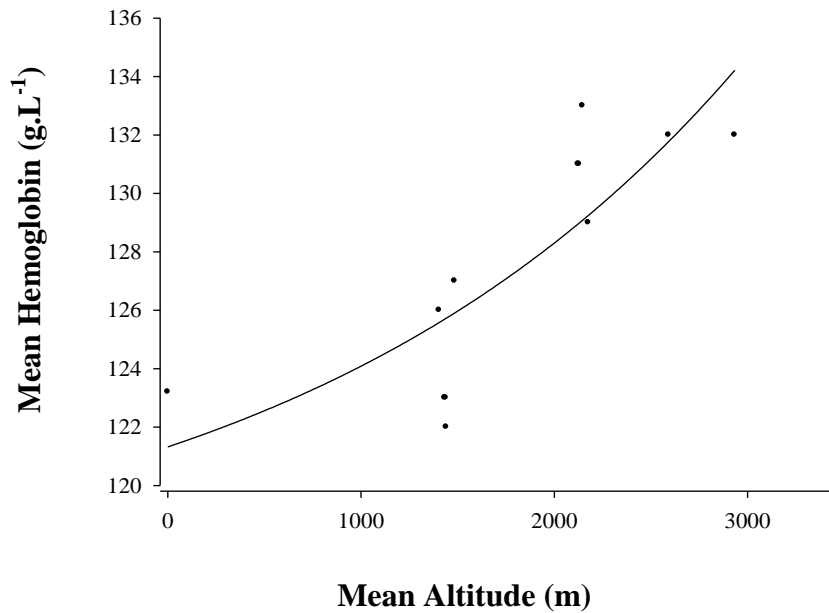
For children the best fit curve was:

$$\text{Hb} = 8.024 \times \exp^{0.00042 * (\text{altitude} - 1000)} + 116.061 \text{ (RMSE=255; } R^2=0.67 \text{) (Figure 2.2)}$$

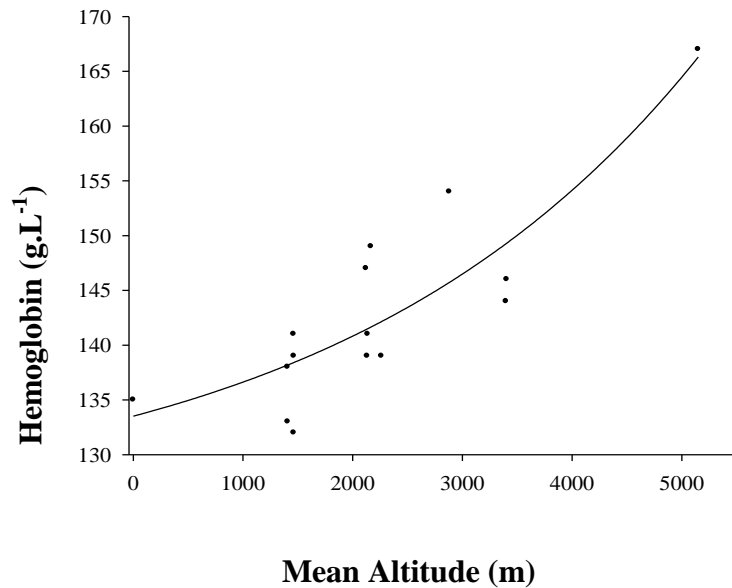
For women the best fit curve was:

$$\text{Hb} = 11.989 \times \exp^{0.0003 \times (\text{altitude} - 1000)} + 124.637 \text{ (RMSE= 320; } R^2=0.75 \text{) (Figure 2.3)}$$

<sup>10</sup> Values used for women and children were taken from the US NHANES III<sup>36, 37, 39</sup>.



**Figure 2.2:** Hemoglobin altitude curve for children 6-59 months for 0 to 3000m



**Figure 2.3:** Hemoglobin-altitude curve for women of childbearing age, for 0 to 5150 meters

Based on these curves that predicted the relationship between hemoglobin and altitude, correction factors for hemoglobin for every 100 meter increase in altitude

above 1000 meters were calculated (Table 2.5 and Table 2.6). Based on these corrections, the first correction to hemoglobin concentration would occur at 1200 meters for both children and women. For children, the rate of correction increased by 1 g/L every 300 meters from 1200-1700 meters and by 1 g/L every 200meters thereafter. For women the rate of increase was varied and no distinct pattern was noticed. The maximum correction applied for children at 3000 meters would be 9 g/L and for women at 5000 meters the maximum would be 24 g/L. These corrections can be either added to the sea level cut-offs for anemia or can be subtracted from individual or population values of hemoglobin based on altitude.

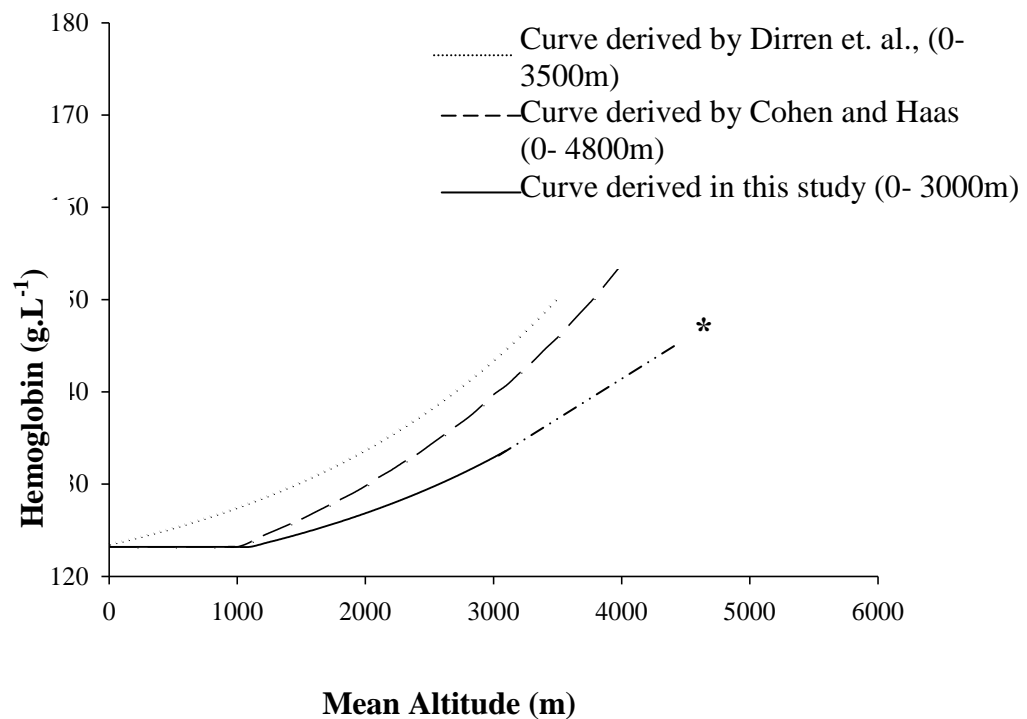
The predicted curves from this study were compared with previous published curves for Andean populations computed by Dirren et al., (1994) and Cohen and Haas (1999) by adding their cutoffs to sea level values for women and children. Figures 2.4 and 2.5 graphically illustrate these comparisons for children and women respectively. Both the Andean-based curves have steeper slopes compared to both the curves for women and children (extrapolated beyond 3000m) derived in this study. Further, the curves in this study attain lower hemoglobin concentrations for each mean altitude level compared to the Andean-based curves previously derived.

## **2.4 DISCUSSIONS**

In this study, we developed an Asian-based altitude correction factor for hemoglobin. We found that, based on the curves derived in this study, corrections for hemoglobin would be applied beginning at altitudes of 1200 meters for both women and children. Corrections increased by 1g/L with approximately every 300 meter increase in altitude for children but with no distinct pattern for women.

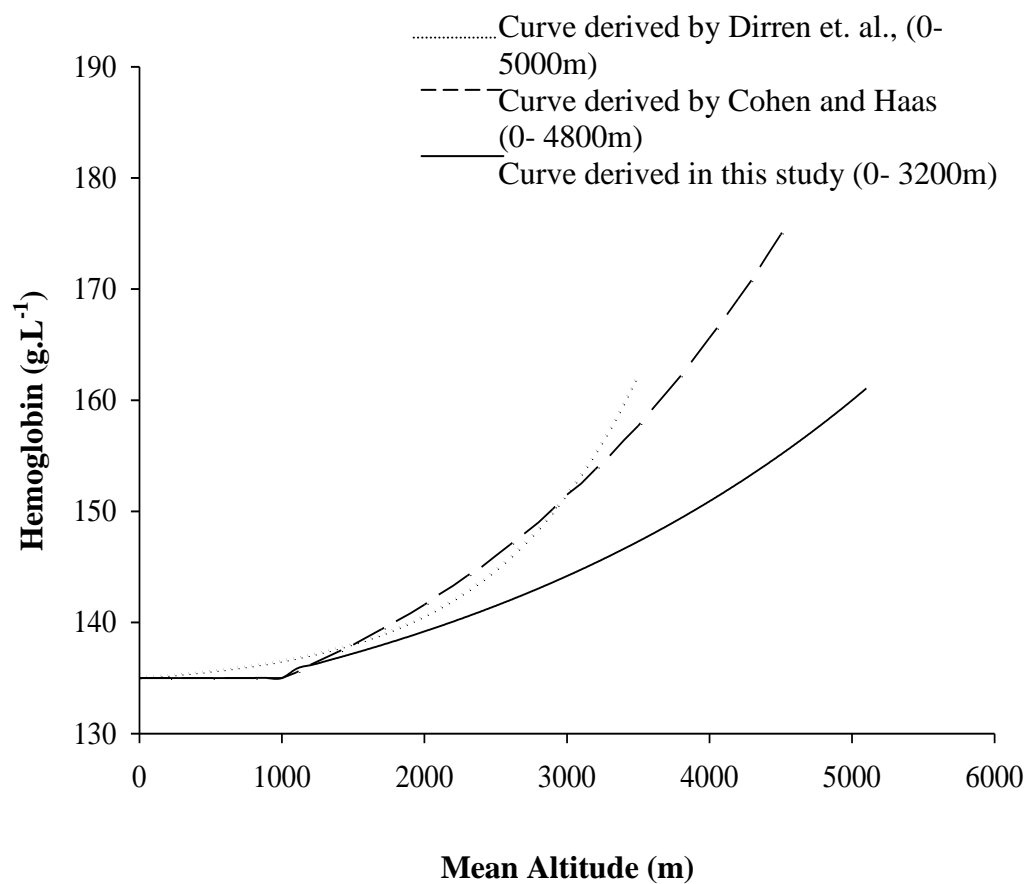
We compared our results to previous correction factors developed by Dirren et al. (1994) and Cohen and Haas (1999) <sup>8, 12</sup>. Our corrections to hemoglobin





**Figure 2.4:** Comparison of derived hemoglobin-altitude curves for children by Cohen and Haas (1999), Dirren et al (1994) and this study

\*The curve for children was estimated using data from 0-3000, the rest of the curve was extrapolated beyond this.



**Figure 2.5:** Comparison of derived hemoglobin-altitude curves for women by Cohen and Haas (1999), Dirren et al., (1994) and this study

**Table 2.5:** Hemoglobin-altitude corrections for children

Altitude orrection (m)		Altitude (m)	Hb Correction ( g/L)
100	0	1600	2
200	0	1700	2
300	0	1800	3
400	0	1900	3
500	0	2000	4
600	0	2100	4
700	0	2200	5
800	0	2300	5
900	0	2400	6
1000	0	2500	6
1100	0	2600	7
1200	1	2700	7
1300	1	2800	8
1400	1	2900	9
1500	2	3000	9

(m)=meters, Hb= Hemoglobin, (g/L)= grams per liters

concentrations changed more gradually with increasing altitude and resulted in overall more moderate reductions in hemoglobin levels. With our curves, the first corrections were applied at 1200 meters, Cohen and Haas,(1999) at 1100 and Dirren et al.'s (1994) at 200m. The similarity between our starting points for correction and that of Cohen and Haas was expected since we used similar methods to address changes below 1000m. However, at 2000 m Dirren et al., (1994) would correct Hb by 10g/L, Cohen and Haas,(1999) by 7 g/L while our correction would only be 4g/L for children and 4g/L for women. At higher altitudes, for women, the differences become more pronounced: at 3000 meters the hemoglobin cut-offs would be 19 g/L , 16.5 and 9 g/L (for both children and women) and at 3500m 26g/L, 23 g/L and 12g/L for Dirren et al., (1994) Cohen and Haas,(1999) and the current study respectively. To illustrate how differences in correction factors may affect prevalence estimates, we used the correction equations derived in each study to adjust the hemoglobin levels of a sample of children living between 1094 and 3647 meters in the Central Asian Republic

**Table 2.6:** Hemoglobin-altitude correction for women

Altitude (m)	Hb Correction ( g/L)	Altitude (m)	Hb Correction ( g/L)
100	0	2600	6
200	0	2700	7
300	0	2800	7
400	0	2900	8
500	0	3000	9
600	0	3100	9
700	0	3200	10
800	0	3300	10
900	0	3400	11
1000	0	3500	12
1100	0	3600	12
1200	1	3700	13
1300	1	3800	14
1400	1	3900	15
1500	2	4000	15
1600	2	4100	16
1700	3	4200	17
1800	3	4300	18
1900	3	4400	19
2000	4	4500	20
2100	4	4600	20
2200	4	4700	21
2300	5	4800	22
2400	5	4900	23
2500	6	5000	24

(m)=meters, Hb= Hemoglobin, (g/L)= grams per liters

**Table 2.7:** Mean Hemoglobin (g/L) and Anemia Prevalence for a sample of 6 to 36 month old children residing at altitudes between 1000 to 3000 meters calculated according to three different methods of correcting for altitude

	Dirren et al (1994)	Cohen and Haas (1999)	This Study
Mean Hb ( SD)	93.9 (18.4)	93.3(18.4)	99.9 (18.2)
Anemia Prevalence (%)*	79.6	80.1	65.8

\*Anemia was defined as hemoglobin less than 110g/L ,SD= standard deviation  
%= percent, Values calculated in this table were based on data on the hemoglobin levels of infants and young children collected in Kyrgyzstan in 2005 and 2006.

of Kyrgyzstan. Applying our hemoglobin correction equation to the sample resulted in an approximately 6 g/L higher mean hemoglobin and a 14% higher anemia prevalence (Table 2.7). Applying Andean based correction factors resulted in lower calculated mean Hb levels and higher anemia prevalence estimates.

Our hemoglobin corrections would result in lower hemoglobin concentrations at a particular altitude and more gradual increases in hemoglobin levels with increasing altitude. Compared to the other Andean-based derived corrections, this pattern more closely models the altitude-hemoglobin variations observed in high-altitude residents of the Tibetan Plateau since the early seventies<sup>14-19</sup>. Based on several studies by Beall, the Tibetan hematological response to chronic hypoxic stress is blunted compared to the Andeans<sup>14-19</sup>. Beall reported that, up to 4000 meters, Tibetan highlander hemoglobin concentrations are only 5% higher than sea-level residents and hemoglobin concentrations were from between 14 to 36 g/L lower than Andeans at similar altitudes<sup>16, 17, 19</sup>. Tibetan hemoglobin concentrations do drastically increase in response to high-altitude hypoxia, however, this occurs at very high altitudes over 4500 meters but values are still comparatively lower than their Andean counterparts<sup>16, 17, 19</sup>.

Differential hematological values between Andean and Tibetan highlanders are a result of their different physiological and morphological responses to hypobaric hypoxic stress. Mean differences in hematological traits are greater than 2 standard deviations<sup>17</sup>. At the root of the differences in hemoglobin concentrations between Tibetans and Andeans are the differences in concentration of the protein erythropoietin. Levels of this protein, responsible for the differentiation of the precursors of red blood cells, are slightly lower in Tibetans than Andeans. In addition to lower hemoglobin concentrations, high resting ventilation, lower oxygen tissue saturation and a lower sea-level hypoxic ventilatory response are the main ways in which the Tibetans differ from Andeans in the adaptive response to chronic high-altitude hypoxia<sup>14-17</sup>.

There are similarities and differences between the derivations of the Andean-based corrections relative to those developed in the present study that are important to note. All three curves were fit using a non-linear exponential model consistent with the non-linear shape of the oxygen-hemoglobin dissociation curve. Although Dirren et al., (1994) assumed an exponential relationship between hemoglobin and altitude beginning at sea-level, Haas and Cohen (1999) did not. We agreed with Cohen and Haas, (1994) that there is no evidence to support a change in the relationship between hemoglobin concentrations and altitude below 1000 meters. However, because the relationship between hemoglobin and altitude is continuous, we provided sea-level anchors for our curves using the NHANES III values (Table 2.4). In addition, we extended the women's curve to 5000 meters using two values previously measured by Beall et al.<sup>14,15</sup>. No such normative values were available at high altitude, in the literature, for children. These additions made our corrections relevant across a wider range of altitudes.

Our choice to use the United States (US) based sea-level hemoglobin values was based on the assumption that Asian non-anemic hemoglobin values were similar. Sea-level hemoglobin values for an Asian sample that met the criteria of truly iron deficient were not available and therefore US values were used. Although Asian values were not available, to gain insight on how our models would behave if sea-level normative hemoglobin levels were varied we conducted sensitivity analyses. Normative sea-level hemoglobin can range depending on various factors, however, taking into account the range of hemoglobin values of our data we varied sea level values between 122.2- 124.2 g/L for children and 132.2-136.6 g/L for women. Our derived relationship between Hb and altitude for children was very sensitive to changes in the sea level value, even changes in the range of 1 to 2 g/L. For children, varying sea level values between 1 and 2 g/L resulted in a mean change in the correction factor at 2000 meters of 2.8g/L and a mean change of 13.4 g/L at 3000 meters. For women, the model was less sensitive, mean changes at 2000m and 3000m were 1 g/L and 4 g/L at 5000 meters (Figures 2.6 and 2.7). This difference was probably due to the greater number of data points for women than for children at higher altitudes.

Based on this sensitivity analysis, we understand that if an Asian normative hemoglobin sea level value was found to deviate by 2 g/L from the US values, the adjustments derived in this study would need to be applied taking into account these variations or the relationship between hemoglobin and altitude redefined with the new sea-level value. It is difficult to assess whether the variations used in our sensitivity analysis truly represent possible Asian sea level values.

Although we do have confidence in the use of the US sea level mean value in our model (there is currently no evidence to suggest that this value is not applicable to

Asian as well as other populations worldwide) our sensitivity analyses did help us further understand the dynamics of our models and underscore the importance of establishing normative values for hemoglobin at sea-level for different ethnic populations to see how they impact our definition of anemia <sup>36</sup>.

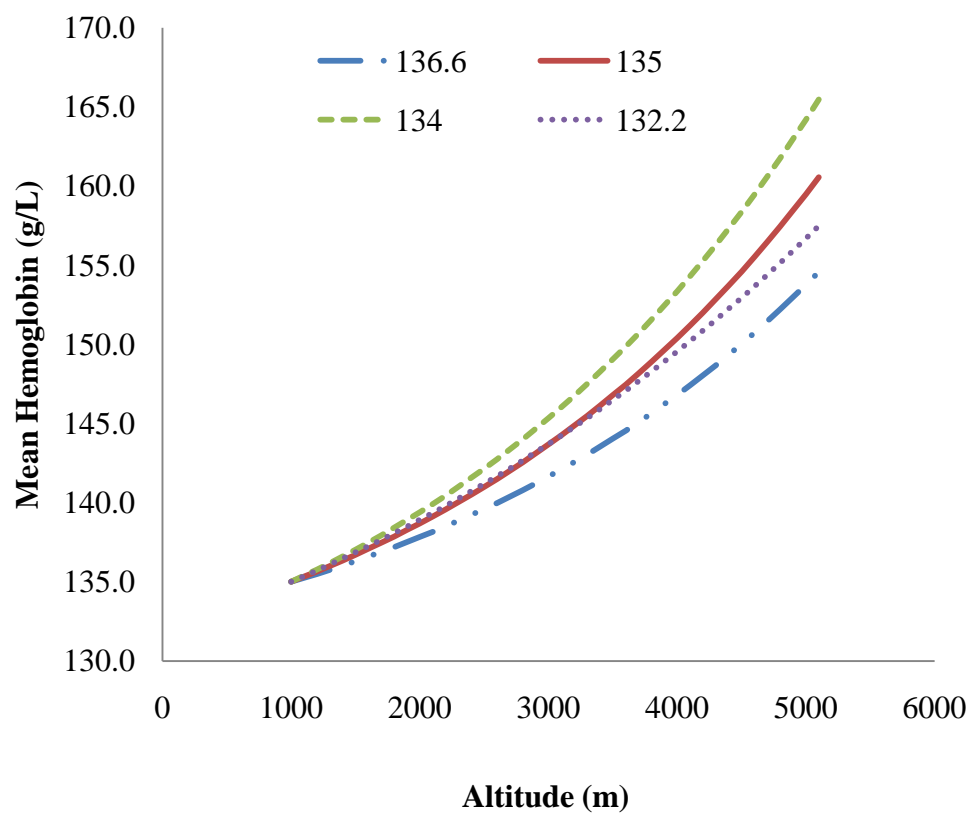
An important difference between the corrections derived in this study and those by Dirren et al., (1994) and Cohen and Haas, (1999) were the hemoglobin values used to establish the hemoglobin-altitude relationships. Dirren et al.'s, (1994) curve was based on Andean children 6 to 59 months that had normal iron status parameters but were not confirmed to be non-anemic. Cohen and Haas, (1999) used data published on mean hemoglobin concentrations of iron-replete women of childbearing age at various altitudes. The non-anemic samples, in this study, were identified from populations with a mixture of both anemic and non-anemic groups. Although we could not verify that our mean hemoglobin values were based only on non-anemics, we used the maximum likelihood estimate method of mixed distribution analysis. This method, when compared to a three-criterion method<sup>11</sup>, accurately estimated the mean and standard deviation of the non-anemic distribution<sup>9</sup>. Further, all sample proportions estimated during analysis were equivalent to or above the reported anemic and non-anemic prevalence for each country. This ensured that, particularly with countries like India where anemia prevalence was high but sample size was large, the influence of anemia on the distribution of the non-anemic was minimized or eliminated.

In addition to anemia, curves based on populations with polycythemia or with hemoglobinopathies (mainly thalassemia) would produce inaccurate estimates of how altitude influences hemoglobin concentrations. For reasons presented in the literature,

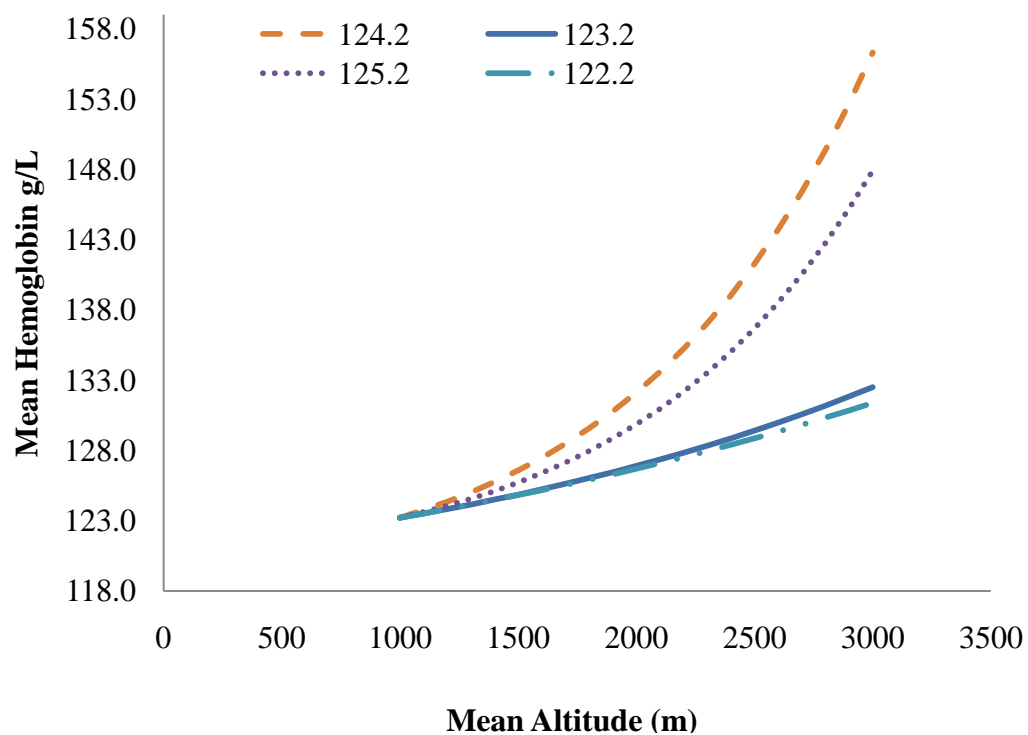
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<sup>11</sup> The three criteria-method of assessing iron status included the use of the indicators serum ferritin , transferring saturation and erythrocyte protoporphyrin.





**Figure 2.6:** Results of sensitivity analysis of variations in sea-level anchor for women



**Figure 2.7:** Results of sensitivity analysis of variations in sea-level anchor for children

the likelihood of the presence of the above hemoglobin abnormalities in our samples was minimal and would not have affected our estimates. The highest hemoglobin values for our sample were well below cut-offs for polycythemia suggested by Tufts et al., (1985). The low prevalence of polycythemia in Tibetan high-altitude residents was later confirmed by Beall et al., (1987), even at altitudes above 5000m. Further, given that the presence of thalassemia is thought to be an adaptation for malaria, these hereditary erythrocytic diseases would be less common populations residing at high-altitudes where the incidence of malaria is low<sup>38</sup>.

This is the first attempt at an Asian based altitude-correction factor for hemoglobin, future studies of this kind can seek to replicate these findings in other Asian populations. We used data from the Demographic Health Surveys with large sample sizes that were adequate for our derivations. At altitudes greater than 3000 meters the sample sizes were smallest, however, we were able obtain good fit to the data and could sufficiently separate the anemic and non-anemic distributions.

The assumption was made that adaptation to hypoxic stress was similar across the countries that were selected. Kyrgyzstan, India and Nepal share common ancestors based on the proximity of the regions to the Tibetan Plateaus that may have created a genetic encapsulation<sup>30, 31</sup>. Armenia was the only country that may have been more distantly related. Analyses were conducted with and without Armenia and based on the R-square values and the standard deviation of the residuals (the fit improved with Armenia) Armenia was retained. Our analysis was limited by the data that were available to us; a benefit of future research in this area would be confirmation of correction factors using data from other countries in Asia. Further studies are needed to confirm these results by adding more data from central Asian populations to the sample; using large sample sizes which would permit the

stratification of the sample into smaller altitude groups which would allow for a more accurate curve with more data points.

The adjustments for hemoglobin at different altitude levels developed in this study can be used in two different ways. They can be added to the recommended World Health Organizations<sup>32</sup> sea-level cut-offs used to define anemia or they can be subtracted from hemoglobin levels measured at a specific altitude<sup>13</sup>. Further, either method can be used to adjust individual hemoglobin levels. For adjustments at the population level it is more accurate to adjust hemoglobin levels of individuals, based on altitude, rather than adjusting a mean value for a population.

## ***2.5 CONCLUSIONS***

Current estimates are that, globally, 2 billion people across are anemic and a large majority of these live in Asia.<sup>1</sup> Further over half of the 140 million people, worldwide, who live above 2500 meters above sea-level, live in Asia. An integral part of addressing this global health challenge of anemia is conducting population-based surveys to estimate the prevalence. The most commonly used approach is the application of a hemoglobin concentration cut-off. Altitude variation is one of the factors that affect hemoglobin levels. Therefore, when assessing anemia in areas with life-long high-altitude residents, hemoglobin must be adjusted.

To date Andean based altitude-correction factors have been used worldwide to adjust hemoglobin. Given that several studies have underscored the presence of more than one model of adaptation to chronic hypobaric hypoxic stress, one correction factor may not suit all. If Asian high-altitude natives exhibit a blunted hemopoietic response to altitude compared to Andeans<sup>14-19</sup>, then using Andean based altitude-correction factors for the definition and classification of anemia in Asia, will incorrectly adjust hemoglobin levels resulting in overestimations of anemia prevalence.

## REFERENCES

1. Kraemer K, Zimmermann M. ed. Nutritional anemia. Basel, Switzerland: Sigh and Life Press, 2007.
2. Baker SJ, DeMaeyer EM. Nutritional anemia: its understanding and control with special reference to the work of the World Health Organization. *Am J Clin Nutr* 1979; 32:368-417.
3. Frisancho AR. Human Adaptation to High-Altitude Environments. In: Anonymous Humankind Evolving: An Exploration of the Origins of Human Diversity. Dubuque, Iowa: Kendall/Hunt, 2006:301.
4. Hurtado, A, Merino, C, and Delgado E. Influence of anoxemia on hemopoietic activity. *Arch Int Med* 1945;75:284-323.
5. Ballew C, Garruto RM, Haas JD. High-Altitude hematology: paradigm or enigma? In: Little, Michael A. Haas, Jere D., ed. Human population biology : a transdisciplinary science. New York : Oxford University Press, 198;338.
6. Tufts DA, Haas JD, Beard JL, Spielvogel H. Distribution of hemoglobin and functional consequences of anemia in adult males at high altitude. *Am J Clin Nutr* 1985;42:1-11.
7. Cook JD, Boy E, Flowers C, Daroca Mdel C. The influence of high-altitude living on body iron. *Blood* 2005;106:1441-6.
8. Dirren H, Logman MH, Barclay DV, Freire WB. Altitude correction for hemoglobin. *Eur J Clin Nutr* 1994;48:625-32.
9. Cohen JH, Haas JD. The comparison of mixed distribution analysis with a three-criteria model as a method for estimating the prevalence of iron deficiency anaemia in Costa Rican children aged 12-23 months. *Int J Epi* 1999;28:82-9.
10. Cook JD, Alvarado J, Gutnisky A, et al. Nutritional deficiency and anemia in Latin America: A collaborative study. *Blood* 1971;38:591-603.

11. Yip R. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. MMWR Recommendations and reports 1998;47:1-29.
12. Cohen JH, Haas JD. Hemoglobin correction factors for estimating the prevalence of iron deficiency anemia in pregnant women residing at high altitudes in Bolivia. Rev Panam Salud Publica 1999;6:392-9.
13. Nestel P. Adjusting Hemoglobin Values in Program Surveys. International Nutritional Anemia Consultative Group, Washington, D.C., (2002).
14. Beall CM, Reichsman AB. Hemoglobin levels in a Himalayan high altitude population. Am J of Phys Anthropol 1984;63:301-6.
15. Beall CM, Goldstein MC. Hemoglobin concentration of pastoral nomads permanently resident at 4,850-5,450 meters in Tibet. Am J Phys Anthropol 1987;73:433-8.
16. Beall CM, Brittenham GM, Strohl KP, et al. Hemoglobin concentration of high-altitude Tibetans and Bolivian Aymara. Am J Phys Anthropol 1998;106:385-400.
17. Beall CM. Adaptations to altitude: A Current Assessment. Annu Rev Anthropol 2001;30: 423-56.
18. Beall CM. Tibetan and Andean contrasts in adaptation to high-altitude hypoxia. Adv Exp Med Biol 2000;475:63-74.
19. Beall CM. Two routes to functional adaptation: Tibetan and Andean high-altitude natives. Proc Natl Acad Sci U S A 2007;104 Suppl 1:8655-60.
20. Anonymous Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. MMWR Recommendations and reports 1998;47:1-29.
21. Everitt B, Hand DJ. Finite mixture distributions. London ; New York: Chapman and Hall, 1981.

22. McLaren CE, Wagstaff M, Brittenham GM, Jacobs A. Detection of two-component mixtures of lognormal distributions in grouped, doubly truncated data: analysis of red blood cell volume distributions. *Biometrics* 1991;47:607-22.
  
23. Lampl M, Johnson ML, Frongillo EA, Jr. Mixed distribution analysis identifies saltation and stasis growth. *Ann Hum Biol* 2001;28:403-11.
  
24. Meyers LD, Habicht JP, Johnson CL, Brownie C. Prevalences of anemia and iron deficiency anemia in Black and White women in the United States estimated by two methods. *Am J Public Health* 1983;73:1042-9.
  
25. Du, J. Combined Algorithms for constrained estimation of Finite Mixture Distributions with Grouped Data and Conditional Data. Master Thesis, McMaster University, 2002.
  
26. Yip R, Strohl KP, Simmons WK. Assessment of the prevalence and the nature of iron deficiency for populations: the utility of comparing haemoglobin distributions. In: Hallberg, L. (Leif) Asp, N.-G Svenska läkaresällskapet., ed. *Iron nutrition in health and disease*. London: J. Libbey & Co., 1996:364.
  
27. Yip R, Johnson C, Dallman PR. Age-related changes in laboratory values used in the diagnosis of anemia and iron deficiency. *The Am J Clin Nutr* 1984;39:427-36.
  
28. Kolsteren P, Atkinson S, Maskall K. Une enquête nutritionnelle au Tibet. *Santé Montrouge, France* 1995;5:247-52.
  
29. Macdonald, P. D. M., Green, P. E. J. User's Guide to Program MIX: An Interactive Program for Fitting Mixtures of Distributions 1988. Ichthus Data Systems, p. 28.
  
30. Su B, Xiao C, Deka R, Seielstad T, Kangwanpong D, Xiao J, Lu D, Underhill P, Cavalli-Sforza L, Chakraborty R, et al. Y chromosome haplotypes reveal prehistorical migrations to the Himalayas. *Hum Genet* 2000;107:582-90.
  
31. van Driem G (2001) *Languages of the Himalayas: an ethnolinguistic handbook of the greater Himalayan region containing an introduction to the symbiotic theory of language*. Brill, Leiden, The Netherlands.

32. WHO (1968). Nutritional Anaemias. WHO Technical Report Series No. 405, World Health Organization, Geneva, Switzerland.
33. Brownie C, Habicht JP. Selecting a screening cut-off point or diagnostic criterion for comparing prevalences of disease. *Biometrics* 1984;40:675-84.
34. Wu T, Wang X, Wei C, et al. Hemoglobin levels in Qinghai-Tibet: different effects of gender for Tibetans vs. Han. *J Appl Physiol* 1985 2005;98:598-604.
35. Estrella R, Hercberg S, Maggy G, Larreategui J, Yopez R. Evaluation of iron-deficiency anemia by an iron supplementation trial in children living at a 2,800-m altitude. *Clinica chimica acta*; 1987;164:1-6.
36. Robins EB, Blum S. Hematologic reference values for African American children and adolescents. *Am J Hematol* 2007;82:611-4.
37. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood* 2006;107:1747-50.
38. Suzuki A, Hamano S, Shirakawa T, et al. The distribution of hereditary erythrocytic disorders associated with malaria, in a lowland area of Nepal: a micro-epidemiological study. *Ann Trop Med Parasitol* 2007;101:113-22.
39. Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL. Prevalence of iron deficiency in the United States. *JAMA*. 1997 Mar 26;277(12):973-6.



## CHAPTER 3

### EPIDEMIOLOGY OF ANEMIA IN 6 TO 36 MONTH OLD CHILDREN IN CENTRAL ASIAN REPUBLIC OF KYRGYZSTAN

#### **3.1 BACKGROUND**

##### **3.1.1 Kyrgyzstan**

The Kyrgyz Republic (Kyrgyzstan) is the second smallest Central Asian state bordered by Kazakhstan, Uzbekistan, Tajikistan, and China. This landlocked country has a terrain that is dominated by 88 mountain ranges belonging to the Pamir-Alai in the south west and the Tien Shan Mountains in the north east. Over 94% of its 195,500 square kilometers are 1000 meters (3280 feet) above sea level and 30% stands 3000 meters (9840 feet) and higher<sup>43</sup>. The economy is mainly supported by industry (lighting, food and manufacturing-building) and agriculture (wool, livestock and fruit and vegetable production) which compromise 37.8% and 28.6% of the Gross Domestic Product respectively (GDP) <sup>47</sup>.

Kyrgyzstan as it exists today has been, to a large extent, shaped by the political dictates of the former Soviet Union. Even the history of Kyrgyzstan and its people (the Kyrgyz) can be divided into three different phases: pre-soviet, soviet and post-soviet. Information on the pre-soviet history of the Kyrgyz in Kyrgyzstan is limited. Archeological findings are indicative of settlements in the Kyrgyzstan territory beginning in the Paleolithic era. However, the origin of the Kyrgyz people remains controversial since many different groups have occupied the region<sup>44-46</sup>. Since the beginning of the Christian era, significant occupants of Kyrgyzstan have been Scythian (Armenian speaking nomadic pastoralists) and Turkic (from the Yenisey in Southern Siberia) tribes who were influenced by Chinese and Mongol invaders<sup>44-46</sup>. Today's Kyrgyz are possibly descendants of these various groups who inhabited the

region up to the middle of the 19<sup>th</sup> century. At the end of this pre-soviet period, the Kyrgyz had developed a distinct language and a culture rooted in a nomadic lifestyle with some Islamic influence<sup>44</sup>.

Policies implemented in Kyrgyzstan during the Soviet era had bittersweet outcomes in Kyrgyzstan. For example although the Soviets introduced a centrally managed health care system that, for a time, effectively delivered sanitary and public health services to the population, the system became increasingly unable to meet the needs of the population which contributed to a deterioration in the population's health status<sup>47</sup>. In addition Russian policies served to undermine the nomadic lifestyle and Islamic beliefs of the Kyrgyz<sup>44, 45</sup>. Overall, for more than 70 years the Soviets had a marked effect on all economic and social aspects of Kyrgyz life which lingered into the present day post-Soviet Kyrgyz environment<sup>44-46</sup>.

In the wake of the collapse of the Soviet Union in 1991, Kyrgyzstan's economic struggles were reflected in the population's health indices: although there have been improvements in some areas a great deal of progress still needs to be made. In the post-soviet environment the country dealt with harsh economic shocks such as the loss of Soviet subsidies which lead to dramatic increases in unemployment and poverty. By 2002 the per capita GDP was \$322 and 44.4 % of the population were living below the poverty line, 70% of whom resided in rural areas and depended on a subsistence income. Presently, although there has been a 5% increase in average GDP per year since 2003 and a decline in poverty by 35%, Kyrgyzstan is classified as a low-income country and with a per capita GNI of \$600, remains among the poorest countries in the world<sup>48</sup>

The major health indicators reflect the economic progression in Kyrgyzstan.

Prior to 1991, having inherited the Soviet Union's system of universal health care, Kyrgyzstan enjoyed better health care than other countries with a similar per capita income<sup>43,47</sup>. The abrupt changes accompanying independence severed ties from the Soviet Union and the ensuing financial crisis resulted in reduced government support of the health system. Kyrgyzstan maintained the free universal health care it inherited from the Soviets but the result has been poorly paid, inadequately trained, medical staff, insufficient medical supplies and facilities that are inadequate as well as unsanitary<sup>47</sup>.

Currently although there is some debate regarding several point estimates<sup>12</sup>, overall trends are that life expectancy has improved since 1994 but is still 10 years lower than in the European Union. There has been a decrease in infant mortality but an increase in maternal mortality<sup>47</sup>. Although underweight, stunting and wasting has decreased to 8.2%, 4% and 14% respectively, major micronutrient deficiencies continue to exist in the population including iodine (85% of children) iron-deficiency anemia (50 % of children under three and 60% of women) and Vitamin A deficiency (32.9% of children less than 5 years old)<sup>13</sup>. With lack of universal access to safe drinking water and sanitation in homes and schools, water-borne infections are common as is Hepatitis B, and blood borne infections. The Republic still experiences infectious diseases such as tuberculosis, brucellosis, sexually transmitted diseases, respiratory infections, and diarrhea, as well as non-communicable diseases such as coronary heart disease, stroke, chronic obstructive pulmonary disease, and cancer<sup>47</sup>. In Kyrgyzstan, since 1991 some progress has been made for example Kyrgyzstan is expected to achieve its poverty and child mortality millennium development goal

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<sup>12</sup> Specific values will not be presented here since in our estimation there is little consensus on the levels of each indicator, however, statistical trends which are the same across the literature will be outlined.

<sup>13</sup> UNICEF [http://www.unicef.org/infobycountry/kyrgyzstan\\_statistics.html](http://www.unicef.org/infobycountry/kyrgyzstan_statistics.html)

targets<sup>48</sup>. However, significant challenges remain such as in the areas of child health which may require a holistic approach than can help resolve the existing problems of malnutrition and micronutrient deficiencies in preschool children<sup>33,36</sup>.

### ***3.1.2 Anemia in Central Asia and Kyrgyzstan***

For decades, anemia has been a global public health problem affecting the lives of many young infants and children. Almost half of the world's preschool aged children are anemic<sup>1,2</sup>. Although anemia can result from a variety of causes, estimates suggest that where the prevalence of anemia is high, about half of anemia is due to iron deficiency<sup>1,3,4</sup>. By 4-6 months many infants require other sources of iron in addition to breast milk to support their rapid growth and development<sup>5,6</sup>. Without sufficient iron in their diets, preschoolers may grow with impaired cognition and behavioral abnormalities<sup>7-9, 30</sup>. Due to its high prevalence and significant impact on child growth and development, anemia continues to be a global health priority requiring specific strategies for its prevention and control.

The greatest numbers of anemic young infants and children reside in Asia<sup>2</sup>. In 1994, the former Soviet ruled Central Asian countries of Kyrgyzstan, Kazakhstan, Tajikistan, Turkmenistan, and Uzbekistan (CARK) adopted a common anemia prevention and control strategy to reduce the prevalence of anemia and iron deficiency among young children<sup>10-13</sup>. Nationally representative prevalence rates of anemia<sup>14</sup> among children less than 3 years of age in Kazakhstan (1995), Uzbekistan (1996) and the Kyrgyz Republic (1997) were reported to be 69%, 61% and 50% respectively<sup>10-13</sup>. Since the nineties CARK's multiple-intervention based anemia prevention and control strategy has been implemented in stages and includes education, research, supplementation of high risk groups and wheat fortification<sup>10-13</sup>.

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<sup>14</sup> Anemia was measured by assessing blood hemoglobin levels of children less 3 years of age.

Anemia control activities in the CARK region, which have focused on iron supplementation and fortification, seem to have had limited impact on preventing and controlling anemia in preschool-aged children. Weekly iron supplementation for children 6 to 24 months old, implemented at the oblast<sup>15</sup> level in each country, was initially successful but overall there was no impact on anemia prevalence levels<sup>11,14</sup>. In Kyrgyzstan reports were not only that desired reductions in morbidity and prevention of IDA were not achieved but in some instances prevalence levels for young children increased<sup>11,15</sup>.

Although prospects of iron-wheat fortification were positive, sentinel studies of fortification programs demonstrated impact for only some vulnerable groups in certain countries. A recent report focused on universal iron-wheat fortification programs, implemented from 2002-2007, and their impact on anemia in 3 central Asian countries (Kazakhstan, Tajikistan and Uzbekistan). Reports were of general decreases in anemia prevalence in children 12 years and younger with the greatest impact in children older than 5 years<sup>16</sup>. Kyrgyzstan was not included in these studies due to issues related to low accessibility to fortified foods. This slow progress suggests a need for country by country analysis of the constraints to anemia reduction and prevention in central Asia.

Available data suggests that among CARK countries, anemia prevention and control strategies have had the least impact on anemia prevalence in children in Kyrgyzstan. The etiology of the high prevalence of anemia in infants and young children in this country has not been clearly characterized. Any further attempts to address anemia must be based on a deeper understanding of the determinants of anemia through the identification of the risk factors contributing to the development of anemia in Kyrgyz infants and young children.

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<sup>15</sup> An oblast is similar to a province or a state and there are 7 oblasts in Kyrgyzstan.

### *3.1.3 Objective*

This analysis of a cross-sectional survey in the Naryn oblast of Kyrgyzstan was undertaken to examine the prevalence and severity of anemia and associated risk factors among children 6 to 36 months. First, we describe the sample according to the socio-demographic (such as age and sex) and food intake variables collected. Second, we identify the prevalence and severity of anemia in the sample and finally define and describe the relationship between the identified socio-demographic and food intake variables and anemia. Knowing that a sound epidemiological understanding of the nature of the problem of anemia is needed to develop effective interventions to prevent anemia in pre-school children, the goal of this analysis was to inform further anemia prevention and control actions focused on reducing and preventing anemia in children 6 to 36 months old in Kyrgyzstan.

## **3.2 SUBJECTS AND METHODS**

### **3.2.1 Study Population**

In 2005, an intervention to address anemia in the Naryn Oblast<sup>16</sup> of Kyrgyzstan was conducted by the Swiss Red Cross as a part of their Kyrgyz-Swiss Health Reform Support Project (KSHRSP). The data from the KSHRSP cross-sectional baseline assessment of children aged 6 to 36 months in At-Bashy, Naryn and Kochkor raions, in the Naryn oblast, were used for this analysis.

### **3.2.2 Data Collection**

One drop of blood from a finger-prick was collected in a HemoCue microcuvette, from each child, and hemoglobin concentration was read directly in the

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<sup>16</sup> An oblast is a kind of country subdivision that is equivalent to a province. There are 8 oblasts in Kyrgyzstan. A raion is an administrative district. In Naryn there are 5 raions: Ak-Tala, At-bashy, Jungal, Kochkor and Tien-Shan. Naryn has a population of 250,000 and At-Bashy has 50,000 inhabitants.

field. No other indicators for iron status were assessed. In addition to a blood samples, socio-demographic and dietary information were collected. Socio-demographic questions included information on the age and sex of the child, the child's family size, level of education attained by the child's mother, meat consumption by the child's mother and household ownership of land and livestock. In addition, dietary information was collected based on mothers' recall of whether or not a child was given a certain food item in 24 hours prior to being surveyed. Additional questions related to the child's level of playfulness and appetite, whether the child had received iron or vitamin A supplements in the months prior to the survey.

#### *3.2.2.1 Digital Mapping and Elevation*

Increased hemoglobin concentration presents a physiological adaptation to lifelong exposure to high altitude <sup>17</sup> and altitude varied considerably in the study communities. To account for this in our analyses, altitude was calculated for each community using global information system (GIS), Fuzzy Gazetteer 2.1 (FuzzyG) and Google Earth 4.2 software. Latitude and longitude coordinates (in decimal degrees) of all communities were found using Fuzzy Gazetteer. Manifold GIS was then used to obtain the altitude (in meters) for each city, using elevation data from Global 30 Arc Second Elevation Data Set (GTOPO30) elevation model. Each community identified on the map was categorized as urban, peri-urban or rural using visual displays in Google Earth. Using a digital ruler, communities in At-Bashy center, Naryn city and Kochkor were categorized as urban. Communities within 5 miles of these urban areas were labeled peri-urban and those greater than 5 miles away were labeled rural.

#### *3.2.2.2 Altitude Correction Factor*

To take into account the effect of altitude on hemoglobin, a correction factor was used to adjust the individual hemoglobin levels of the children in this sample

based on altitude. Several correction factors for hemoglobin have been developed based on Andean populations living at high altitudes<sup>18,19, 42</sup>. These correction factors can potentially over-estimate the effect of altitude on hemoglobin in Central Asian populations<sup>20</sup>.

Tibetans (populations residing at the highest levels in the Himalayans) and Andean high-altitude natives undergo dissimilar functional adaptations to offset hypoxic stress<sup>20</sup>. The major differences are that as altitude increases, hemoglobin levels for Asians increase less than Andean populations. One of the major implications for this difference has been in assessing the nutritional status of high-altitude residents; particularly with regards to the definition and identification of anemia.

Consequently, in a previous work, a new correction factor was developed that was appropriate for use with high-altitude residents of central Asia<sup>17</sup> (a). This correction factor was used in this study to adjust the individual hemoglobin levels of each child in the sample.

$$\text{Hb} = 8.024 \times \exp^{0.00042 * (\text{alt} - 1000)} + 116.061 \text{ (a)}$$

### ***3.2.3 Data Analysis***

Data were analyzed using SPSS 15.0 and SAS 9.1. Descriptive statistics included frequencies, means and standard deviations for household and dietary variables. Spearman's correlations and cross-tabulations were used to study the patterns of relationships among different household and food variables. Dietary variables were categorized into one of 4 food groups: carbohydrates, high proteins, milk, fruits and vegetables. Within each group, spearman's correlations and cross-tabulations were used to define relationships among variables.

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<sup>17</sup> See Chapter 1



Anemia was defined in this analysis as a hemoglobin value less than 110 g/L based on the recommended cutoff defined by the World Health Organization (WHO) for children from 6 months to 5 years old <sup>21</sup>. Bivariate analysis revealed a significant relationship between hemoglobin and age, consequently all subsequent analyses were adjusted for age.

Regression analyses were conducted to identify sample characteristics predictive of hemoglobin level and anemia after adjusting for altitude. The existence and strength of relationship between variables were defined using F-tests and chi-squared tests.

### **3.3 RESULTS**

The sample was comprised of 745 children between the ages of 6 and 36 months. The mean age was 20.2 months (Table 3.1). The majority of the children were boys, 424 (57.1%) and 42.9% were girls. The mean altitude at which the children resided was 2129 meters. After correcting for altitude, mean hemoglobin level for the sample was 99.9 g/L.

The majority of the sample lived in rural households (51.8%) and approximately equal amounts lived in urban (26.5%) and peri-urban (21.6%) areas. Over 2/3 of the households owned sheep/goats or cows/horses and 68.7% worked on land that was leased. Within each household, the average number of inhabitants was 5.6. Four hundred and fifty-five (61.2%) of the mothers reported having completed the 10<sup>th</sup> grade. Regarding mothers' level of education, 21.2 percent (159) attended technical college and 15.6% (116) graduated from university (data not shown) . Only 35.3% of the mothers reported eating meat daily and 41.0% ate meat once in three days prior to the survey (Table 3.2).

Most of the children sampled (686, 92.9%) had not had any iron supplements

**Table 3.1:** Sample Characteristics

Variable	N	Mean	Std. Dev.
Age (months)	745	20.2	8.6
Altitude( meters)	745	2129.4	240.7
Hemoglobin (g/L)*	742	99.9	18.2
Family size	742	5.6	1.6

Hemoglobin values were adjusted to sea-level values using a correction factor (See methods). (g/L)= grams per liters, std. dev.= standard deviation, N= sample size

in the month prior to the survey( Table 3.2), however, 695 (93.7%) had received vitamin A supplements ( data not shown). The majority (453, 61.2%) were characterized by their mother as having had a good appetite. Similarly, mothers described 61.9% (456) of the children as being active (Table 3.2).

Foods children were fed 24 hours prior to the survey were categorized into the following food groups: milk, carbohydrates, high protein and fruits and vegetables.

In the 24 hours prior to the survey, most of the Kyrgyz sample consumed cow's milk (84.1%). Breast milk (36.9%), bulamyk (13.6%) and formula (9.3%) were also consumed but by fewer children (Figure 3. 1). Bulamyk is a food fed only to children and is made of flour cooked with clarified butter (sary mai) and milk<sup>33</sup>.

Significantly more of the 6 to 12 month old children drank breast milk (74.2%) compared to the 12 to 24 month olds (36.3%) and the 24-36 month olds (10.9%) ( $p<0.05$ ). A similar intake pattern was seen with bulamyk and formula, ie., considerably less being consumed as age increased ( $p<0.05$ ). For the majority, children drank breast milk with formula but not with cow's milk. At 6 to 12 months there was a significant negative correlation ( $p<0.001$ ) between breast milk and cowmilk intake. This pattern of substitution continued into the 12 to 24 month age group but no longer existed after children were older than 24 months.

**Table 3.2:** Characteristics of Study Sample by Hemoglobin and Anemia groups

Variable	All N(%)	Mean Hb±SE	P*	Percentage of children anemic with:				P*
				Mild	Moderate	Severe	Total	
<b>Place of Residence</b>			0.000					0.000
Urban	197(26.5)	102.5±1.4		22.8	25.9	4.1	52.8	
Peri-urban	160(21.6)	95.5±1.5		16.3	43.1	7.5	66.9	
Rural	385(51.8)	93.5±1.1		18.7	46.8	6.5	71.9	
<b>Mother's Meat Consumption</b>			0.013					0.183
None in past 3 days	175(23.6)	92.9±1.5		20.6	42.9	9.1	72.6	
Once in past 3 days	304(41.0)	96.4±1.2		17.8	42.4	4.9	65.1	
Daily	262(35.3)	97.9±1.3		20.2	36.6	5.3	62.2	
<b>Sheep/ goat</b>			0.000					0.003
None	244(32.2)	95.6±1.3		19.3	39.8	7.0	66.0	
1 to 5	184(25.1)	93.0±1.4		17.9	48.9	8.2	75.0	
6 to 20	222(30.2)	98.2±1.4		21.2	37.8	5.0	64.0	
>20	84(11.4)	101.6±2.1		9.9	8.1	4.4	22.5	
<b>Altitude Groups</b>			0.016					0.14
1000-1500m (m)	4(.5)	87.6±8.9		50.0	50.0	0.0	100.0	
<b>Table 3.2 ( Continued)</b>								
1501-2000 m	129(17.4)	95.5±1.7		22.5	40.3	7.0	69.8	
2001-2500 m	597(80.3)	96.8±1.0		18.5	39.9	5.7	64.1	
>2500m	13(1.7)	81.8±4.9		15.4	61.5	15.4	92.3	
<b>Child's Appetite</b>			0.000					0.000
Extremely good	23(3.1)	106.5±3.7		13.0	30.4	0.0	43.5	
Somewhat good	430(58.1)	99.4±1.1		19.3	39.1	2.8	61.2	
Neither good nor bad	198(26.8)	94.0±1.4		21.2	44.4	8.1	73.7	
Somewhat bad	71(9.4)	87.6±2.2		16.9	39.4	18.3	74.6	

**Table 3.2 ( Continued)**

Extremely bad	18(2.4)	84.2±4.1		11.1	44.4	22.2	77.8	
<b>Child's playfulness</b>			0.000					0.000
Extremely active	45(6.1)	107.9±2.6		22.2	15.6	2.2	40.0	
Somewhat active	411(55.7)	98.7±1.1		19.5	39.7	3.4	62.5	
Neither active nor inactive	211(28.5)	93.6±1.3		20.9	46.4	6.2	73.5	
Somewhat inactive	53(7.2)	83.4±2.4		7.5	45.3	26.4	79.2	
Extremely inactive	18(2.4)	87.8±4.0		16.7	33.3	16.7	66.7	
<b>Iron Supplements</b>			0.03					
Yes	53(7.1)	101.3±2.5		15.1	26.4	5.7	47.2	0.028
<b>Rice</b>			0.038					0.070
Yes	231(31.1)	94.3±1.3		17.7	47.2	4.3	69.3	
No	511(68.9)	97.2±1.1		20.0	37.4	6.8	64.2	
<b>Fruit</b>			0.001					0.001
Yes	434(58.5)	97.9±1.1		19.8	38.2	3.7	61.8	
No	308(41.5)	93.5±1.3		18.5	43.5	9.4	71.4	
<b>Meat</b>			0.000					0.001
Yes	481(64.8)	97.9±1.1		20.4	37.8	4.2	62.4	
No	261(35.2)	92.6±1.3		17.2	45.2	9.6	72.0	
<b>Egg</b>			0.118					0.007
Yes	143(19.3)	94.2±1.6		12.6	52.4	4.2	69.2	
No	599(80.7)	97.0±1.0		20.9	37.6	6.5	64.9	
<b>Wheat</b>			0.000					0.000
Yes	506(68.2)	96.01±1.0		17.4	45.7	6.5	69.6	
No	236(31.8)	102.2±1.4		23.3	29.2	5.1	57.6	
<b>Formula</b>			0.053					0.627
Yes	69(9.3)	96.0 ±1.0		19.0	41.0	6.2	66.3	
No	673(90.7)	100.3±2.3		21.7	34.8	4.3	60.9	
<b>Cow's milk</b>			0.024					0.022

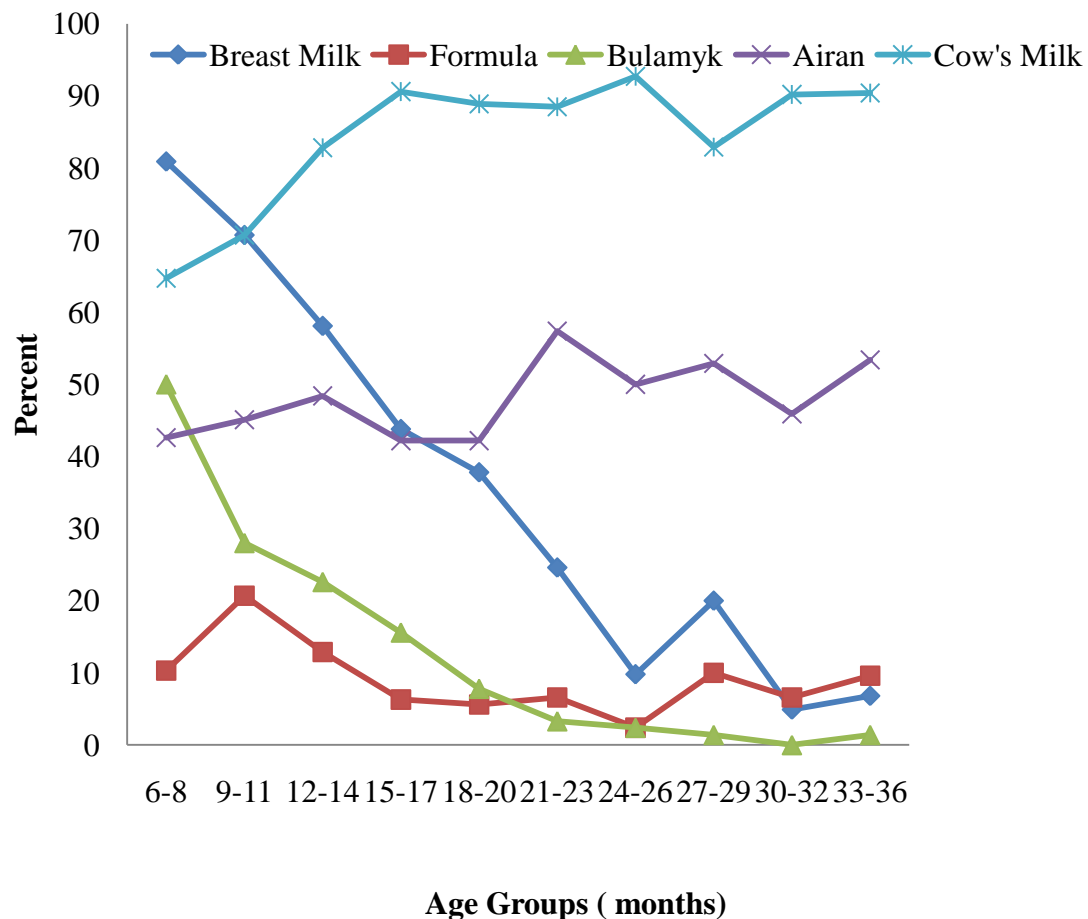
**Table 3.2 ( Continued)**

Yes	624(84.1)	95.8±1.0		17.8	42.1	6.6	66.5	
No	118(15.9)	100.0±1.9		27.1	31.4	3.4	61.9	
<b>Breastmilk</b>			0.048					0.975
Yes	274(36.9)	98.4±1.5		18.6	40.5	5.8	65.0	
No	468(63.1)	95.3±1.1		19.7	40.4	6.2	66.2	
<b>Bulamylk</b>			0.034					0.239
Yes	101(13.6)	92.1±2.2		19.8	46.5	7.9	74.3	
No	641(86.4)	96.5±1.0		19.2	39.5	5.8	64.4	
<b>Total</b>	<b>742</b>	<b>99.9±18.2</b>		<b>19.3</b>	<b>40.4</b>	<b>6.1</b>	<b>65.8</b>	

\* Age-adjusted p-values

Carbohydrates were commonly consumed by the children in the sample noodles (68.6%), biscuits (74.6%), wheat (68.1%) and rice (31.0%) (Figure 3.2). Intake of noodles, wheat and potatoes significantly increased across age groups ( $p < 0.05$ ). In the 24-36 month age groups noodles, wheat and potatoes were eaten by 75.9%, 73.9% and 80.2% of the children respectively. Intake of rice increased significantly across age groups although it was not eaten by as many children as the other foods in the carbohydrate group (only 31.0%).

A majority (64.8%) of the children ate meat 24 hours prior to the survey (Figure 3.3). The percentage of children eating meat increased significantly across age groups with 48.9% of children 6 to 12 months; 69.6% of children 12 to



**Figure 3.1:** Reported consumption of milk-based foods in the past 24 hours

24 months and 71.2% of children 24 to 36 months eating meat ( $p<0.05$ ).

Fruits and vegetables were eaten by 58.5% and 40.7% of the sample. Intake increased significantly across age groups (Figure 3.4) ( $p<0.05$ ).

There was a highly significant J-shaped relationship between hemoglobin and age ( $p<0.001$ ). Mean hemoglobin decreased as children's age increased from 6 to 17 months. After 18 months the children's hemoglobin increased until reaching a mean of 110.17g/L. Mean hemoglobin versus age trends were similar for boys and girls (Figure 3.5). Given the strength of this relationship all bi-variate relationships tested between hemoglobin and other child characteristics we adjusted for non-linear age effects using a second order polynomial model.

Prevalence of anemia was high and slightly severe (Table 3.2) with more than half of the children (65.8%) having some level of anemia. The majority of the children (40.4%) who were anemic had Hb values between 70-99 g/L and were classified as moderately anemic (Table 3.2). Prevalence of severe anemia (Hb levels less than 70 g/L) was 6.1%.

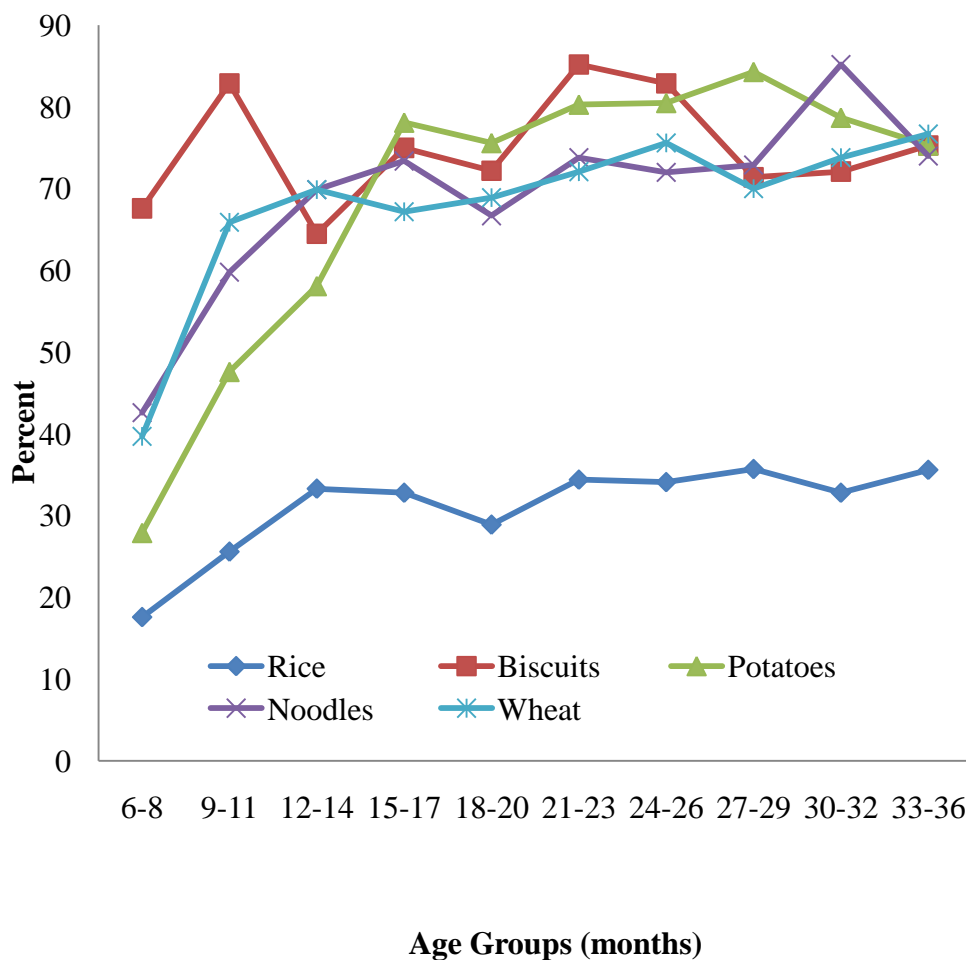
### 3.3.1 Risk Factors for anemia

#### ***3.3.1 Risk Factors for anemia***

In age-adjusted bivariate analyses, several of the household demographic variables were significantly associated with hemoglobin levels (Table 3.2). Hemoglobin (Hb) levels of the children decreased according to place of residence i.e., urban residents had significantly higher Hb levels than rural residents ( $p<0.001$ ). Hemoglobin levels increased as the frequency of mothers' meat intake in the 3 days prior to the survey increased ( $p= 0.013$ ). Mean hemoglobin varied with ownership of sheep or goats (Table 3.2) but there was no association between children's hemoglobin and family ownership of cows or horses (data not shown). Even using altitude-adjusted hemoglobin values, altitude of residence remained associated with hemoglobin levels, perhaps reflecting other social or lifestyle characteristics



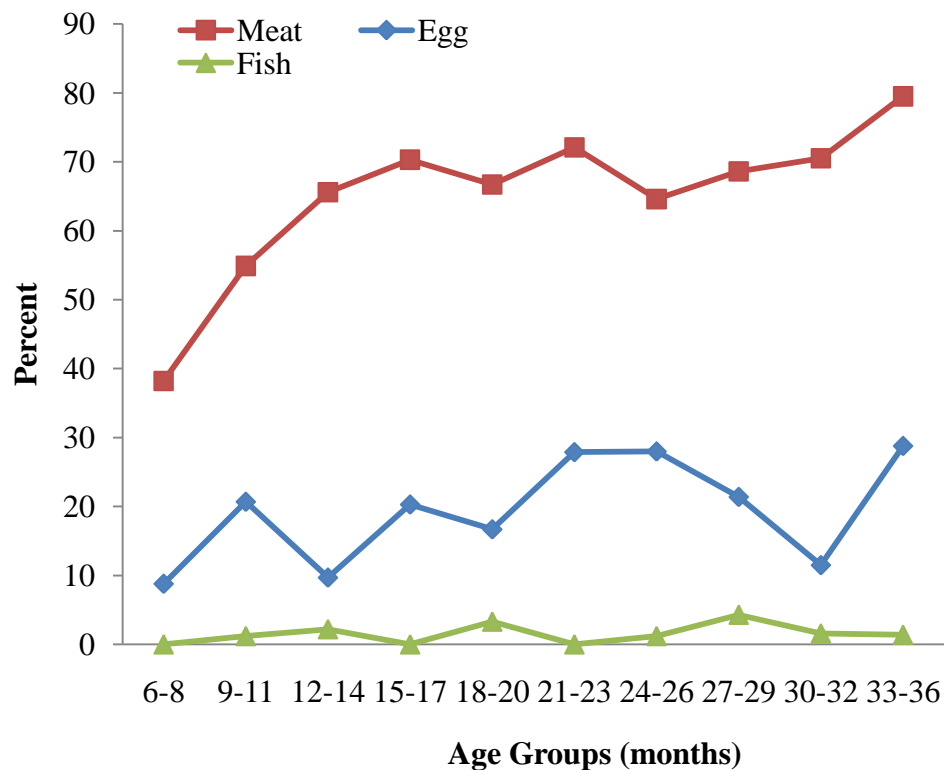
associated with altitude. Children residing at the lowest and highest altitudes had lower hemoglobin levels than those residing between 1500 and 2500m ( $p=0.016$ ). Hemoglobin levels significantly increased as the level of children's appetites ( $p<0.001$ ) changed from extremely bad to extremely good (as assessed by their mothers) and when the level of children's playfulness ( $p<0.001$ ) changed from extremely inactive to extremely active. Children who had intake of iron syrup prior to the survey ( $p=0.03$ ), meat ( $p<0.001$ ), fruit ( $p=0.001$ ) breast milk ( $p=0.048$ ) and formula ( $p=0.053$ ) had higher hemoglobin levels than children who did not.



**Figure 3.2:** Reported consumption of carbohydrate foods in the past 24 hours

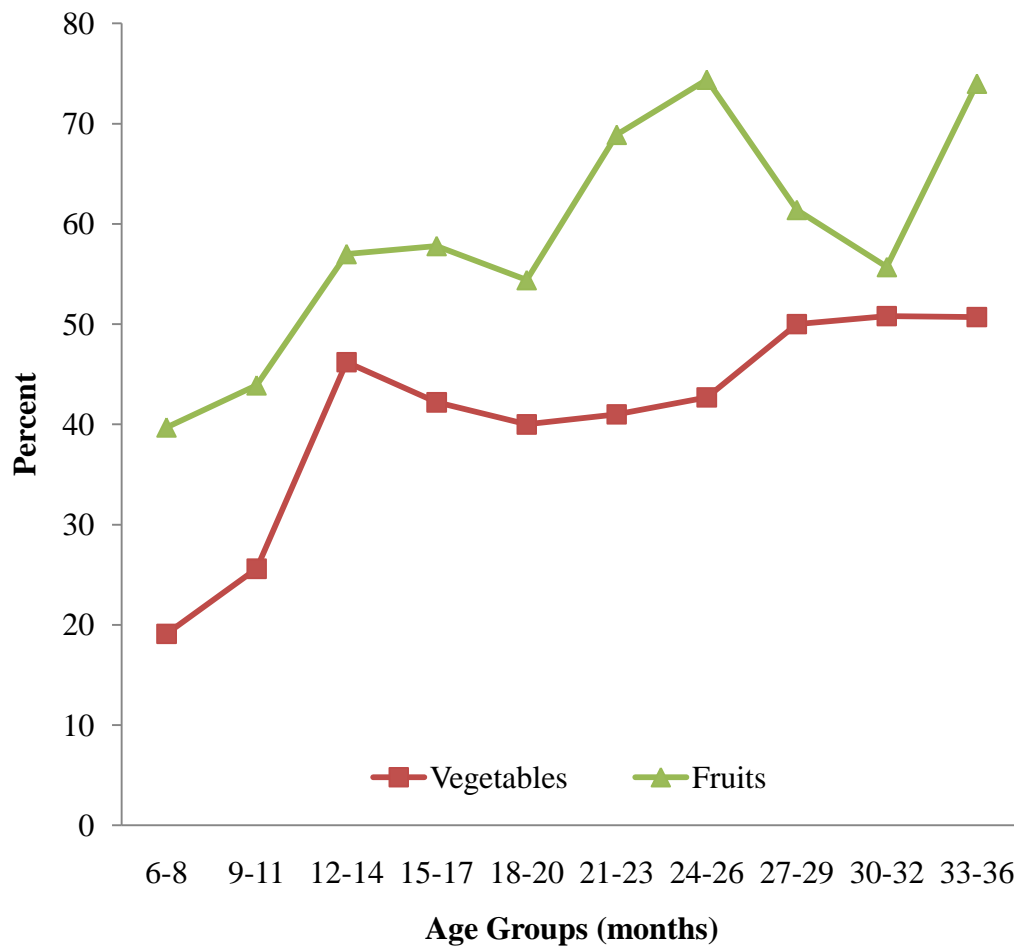
Having rice ( $p=0.038$ ), wheat ( $p<0.001$ ), cow's milk ( $p=0.024$ ), and bulamyk ( $p=0.034$ ) was significantly associated with lower hemoglobin levels.

Anemia was positively associated with place of residence ( $p<0.001$ ) ownership of sheep/goats ( $p=0.003$ ). Mother's were also asked to about their perceptions of their child's level of playfulness and appetite level. Perceptions of children's behavior were



**Figure 3.3:** Reported consumption of high protein foods in the previous 24 hours by age

significantly positively associated with mean hemoglobin levels ( $p<0.001$ ). Children whose mother's reported that they had extremely good appetites or who were extremely active, had the highest mean hemoglobin levels. As mothers' assessments of their children's appetites went from extremely good to extremely bad, the associated mean hemoglobin levels of their children decreased. A similar decrease in mean



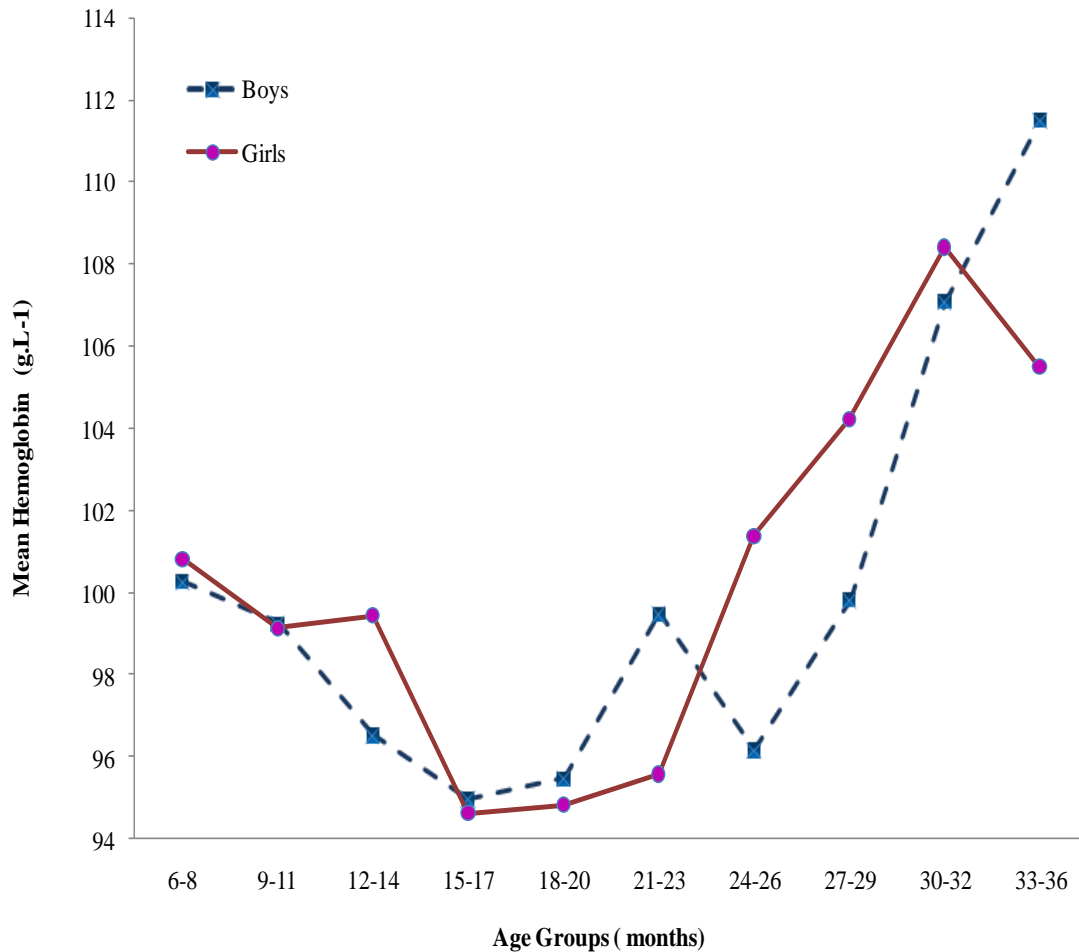
**Figure 3.4:** Reported consumption of fruits and vegetables in the previous 24 hours by age

hemoglobin was observed as mothers' perception of child's level of playfulness went from extremely active to extremely inactive.

A significantly lower percentage of children who had received iron supplements ( $p=0.028$ ), fruits ( $p=0.001$ ) and meat ( $p=0.001$ ) were anemic (Table 3.2). Higher percentages of children who ate rice ( $p=0.070$ ), eggs ( $p=0.007$ ), wheat ( $p<0.001$ ) and cow's milk ( $p=0.020$ ) were anemic.

In multivariate regression models, significant predictors of hemoglobin levels were age, urban/ rural residence, ownership of sheep or goat, and intake of meat, formula, noodles, bulamyk, fruit and cow's milk. The J-shaped age relationship seen in Figure 3.5 remained essentially unchanged in the multivariate model.

Children living in urban areas had significantly higher hemoglobin levels than those residing in peri-urban ( $p<0.001$ ) or rural areas ( $p=.007$ ) although there was no significant difference between Hb levels of those living in rural or peri-urban areas.



**Figure 3.5:** Mean hemoglobin by age and sex

Families owning no sheep/goats versus owning 1 to 5 sheep/goats made no significant difference in the hemoglobin levels of children. However, Hb levels for children whose families owned no sheep/goats were significantly lower than those who owned greater than 20 sheep/goats ( $p=0.01$ ). Families with 1 to 5 sheep/goats had children with significantly lower Hb levels than those with 6 to 20 ( $p=0.02$ ) and greater than 20 sheep or goat ( $p=0.004$ ).

Children who had consumed meat ( $p=0.01$ ), formula ( $p=0.03$ ), fruit ( $p=0.04$ ) and noodles ( $p=0.03$ ) had significantly higher hemoglobin levels than children who had not. Conversely, children who had eaten bulamyk ( $p=0.04$ ) and drank cow's milk ( $p=0.03$ ) had lower hemoglobin levels than children who had not.

Significant predictors of anemia were age ( $p=0.000$ ), intake of meat ( $p=0.07$ ), fruit ( $p=0.06$ ), breast milk ( $p=0.03$ ) and biscuits ( $p=0.02$ ). Risk of anemia was lower for children who ate meat (31%), fruit (31%) or drank breast milk (38%). Risk increased with consumption of biscuits (45%) (Table 3.3).

### **3.4 DISCUSSION**

The prevalence of anemia in our sample of 6 to 36 month old children living in the Naryn oblast of Kyrgyzstan was 65.8%. This prevalence of anemia was higher than the levels found in the Kyrgyzstan Demographic and Health Survey (KDHS) assessment in 1997. In order to compare our report to the KDHS results, hemoglobin levels for children between 6 and 36 months, from the 1997 KDHS, were adjusted for altitude with the central-Asian based correction factor used in this analysis. Based on this process, the anemia prevalence among children 6 to 36 months in the KDHS 1997 sample in Kyrgyzstan was found to be 43.3% with equal amounts of moderate (20.7%) and mild anemia (20.9%). Severe anemia prevalence was 1.7%. In our sample, most of the anemia was moderate (40.4%) only 19.3% was mild and 6.1% was severe. Our sample was, however, was not nationally representative and during data collection investigators may have selected regions where the anemia prevalence was higher than the national average. Based on this comparison, in *some areas* of Kyrgyzstan not only is anemia still an important problem in preschool children but prevalence has increased and become more severe over the past 10 years.

**Table 3.3:** Predictors of hemoglobin concentration and anemia from multivariate models

<b>Variables</b>	<b>Mean hemoglobin ( 95% CI)<sup>c</sup></b>	<b>P value</b>	<b>Odds ratio (95% CI) for anemia risk<sup>b</sup></b>	<b>P value</b>
Age	<b>0.16 (-0.009-0.33)</b>	<b>0.05</b>	<b>0.96 (0.95-0.98)</b>	<b>0.000</b>
Age*Age	<b>0.05 (0.03-0.07)</b>	<b>0.000</b>	<b>0.99 (0.99-1.00)</b>	<b>0.000</b>
<b><i>Meat</i></b>		0.011		0.07
No	<b>95.2 (91.6 -98.7)</b>		1	
Yes	100.1 (94.9-105.4)		<b>0.69 (0.48-0.99)</b>	
<b><i>Fruit</i></b>		0.043		0.06
No	<b>96.3(92.1 100.6)</b>		1	
Yes	99.0 (95.0-103.0)		<b>0.69 (0.47-1.02)</b>	
<b><i>Breastmilk</i></b>				0.03
No			1	
Yes			<b>0.62 (0.41-0.94)</b>	
<b><i>Biscuit</i></b>				0.02
No			1	
Yes			<b>1.45 (1.06-1.99)</b>	
<b>Place of Residence</b>		0.019		
Urban	<b>102.9 (96.8-109.0)</b>			
Peri-urban	95.6 (90.6-100.6)			
Rural	94.5 (90.6- 98.3)			
<b>Ownership of Sheep/ goat</b>		0.004		
None	<b>95.6 (91.4-99.7)</b>			
1 to 5	<b>94.6 (90.2- 99.0)</b>			
6 to 20	98.5 (94.1-102.9)			
>20	102.0 (96.8-107.2)			
<b><i>Formula</i></b>		0.028		
No	<b>95.2 (91.6-98.7)</b>			
Yes	100.1 (94.9-105.4)			
<b><i>Cow's milk</i></b>		0.026		
No	<b>99.6 (94.8-104.4)</b>			
Yes	95.7 (92.0 - 99.4)			
<b>Bulamyk</b>		0.043		
No	<b>99.8 (96.1-103.4)</b>			
Yes	95.6 (90.5-100.6)			

**Table 3.3 (Continued)**

<b>Noodles</b>		0.034
No	<b>96.2 (91.9-100.5)</b>	
Yes	99.2 (95.2-103.2 )	

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a. Individual Hb values are adjusted for altitude, b. Anemia is defined as Hb <110 grams per liters

c. Mean Hb values are predicted for a child age 20.2 months, which was the mean value for the sample



Prior to 6 months an exclusively breastfed, full-term infant should have adequate stores to meet iron needs<sup>5-6, 22-25</sup>. Assuming that the infants are full-term<sup>18</sup>, the significant relationships between age and anemia and Hb levels observed in our sample indicate that the children's daily environment may not be supportive to the intake of adequate bio-available iron to meet their increased needs from a very early stage in infancy. We found that anemia prevalence was already high at 6 months (similar to other recent findings<sup>50</sup>.) If in Kyrgyzstan, young infants are exposed to an environment where there are low levels of exclusive breastfeeding practiced and high rates of early introduction of liquids such as teas and milk, these factors may have contributed to the already high anemia prevalence observed in our sample at 6 months.

Early infant feeding practices are important determinants of micronutrient status of preschoolers. Data on the infant feeding practices that existed before, during or after Soviet involvement in Kyrgyzstan are limited. However, some evidence on Soviet nutrition policies may give some insight on the kind of feeding practices young infants in Kyrgyzstan may have experience during the Soviet era. Conclusions of a 2002 review investigating the feeding practices of the Central Asian States and countries of the former Soviet Union were that Soviet nutritional recommendations differed from international standards<sup>36</sup>. Feeding practices in the Central Asian Republics (including Kyrgyzstan) included: low levels of exclusive breastfeeding<sup>19</sup>, early introduction (earlier than 4 months) of teas, cow's milk, semi-solid foods (e.g. curds, kefir and egg yolk) and the late introduction of meat and liver<sup>36</sup>. In support of these findings, results from the 1997 KDHS showed that for children less than 4 months only 31% were exclusively breast fed, 17% and 51% received water and other

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<sup>18</sup> Approximately 7% of all births in Kyrgyzstan are classified as low birth weight (less than 2500g)

<sup>19</sup> During this period recommendations for the optimal duration of exclusive breastfeeding were for from 0 to 4 months.

supplements respectively; 10% received infant formula as a supplement to breast milk and 34% received teas. Further, a high proportion of all non-breastfed children of all ages received milk and meat/fish/poultry and eggs at around 8-11 months<sup>49</sup>. These findings suggest that nutrition policies and recommendations instituted during the Soviet era may have had (and perhaps continued to have in the post-Soviet era) a negative impact on the nutritional status of Kyrgyz young infants.

Late introduction of iron enhancing complementary foods such as meat in Kyrgyzstan may serve to perpetuate the risk of anemia begun in early infancy<sup>36,49</sup>. In our sample, anemia risk increased further between 6 and 24 months. Six to 24 months of age has been characterized in the infant and child feeding literature as a period of increased risk of IDA. During this period, iron requirements increase due to accelerated growth and development and children must be fed the appropriate quantity and quality of complementary foods, in addition to breast-milk, in order to adequately meet iron needs<sup>6, 26-29</sup>.

One food that is high in iron and contributes to positive iron absorption is meat. Meat consumption was reported to have declined in the Central Asian Republics after the collapse of the former Soviet Union. Authors of a WHO 2000 review of complementary feeding practices in former Soviet Republics hypothesized that decreased meat availability may have influenced the late introduction (8 to 9 months) of meat as a complementary food. However, even though post-soviet meat availability was estimated at 30-40kg/person/year, in 2000, this amount, which is considerably less than the former Soviet Union's target of 80kg/person/year, it is still relatively accessible and meat consumption was reduced but not eliminated<sup>33</sup>.

Contrary to the reported reduction in meat consumption in the Central Asian Republics, in our sample a large percentage of children (64.8%) were fed meat 24 hours prior to the survey. Children who ate meat had average hemoglobin values that

were 3.5 g/l greater than children who did not eat meat. Further, children who ate meat had a 31% lower risk of developing anemia. Nonetheless, anemia prevalence was still high (60.1%) among children who were fed meat in this sample. Meat consumption by young infants and children was also reported in the 1997 KDHS. Both breastfed (35.6%) and non-breastfed (69.7%) children between 4 to 35 months received meat 24 hours prior to the survey<sup>49</sup>.

Quantity, quality and frequency of meat intake are all important factors for iron status. Brown et al., (1998) after calculating the amounts of iron-rich food needed from complementary foods concluded that providing children with iron from unfortified complementary foods alone to meet their requirements would be difficult<sup>26</sup>. Even with a highly iron-rich meat such as liver, children would still require larger intake amounts than are normally consumed<sup>26</sup>. It is possible that the children in this sample who consumed meat were not fed the bio-available meats in the right quantities and frequencies. Further, these meats may have been consumed with foods that formed insoluble complexes with heme-iron such as calcium and phosphorus<sup>34, 35</sup>.

In addition to meat, cow's milk was consumed by over 80% of the sample. Both the KDHS and the WHO review of complementary feeding report that by the age of 4 months some breastfed children (13%) and over 80% of non-breastfed children are fed cow's milk<sup>33, 36, 49</sup>. In our sample, a large percentage (69.7) of children between 6 and 12 months were given cow's milk. Cow's milk was not predictive of anemia; however, it was negatively associated with hemoglobin levels in the sample and predictive of lower mean hemoglobin levels among children who consumed it. Further, cow's milk was fed to children in this sample as a substitute for breast milk.

Current recommendations are that cow's milk should not be consumed by children in the first year of life<sup>23</sup>. Milk contains calcium and phosphoproteins that inhibit the uptake of both heme and non-heme iron<sup>27, 28, 34, 36</sup>. Estimates are that 165

mg of calcium as milk can result in a 50-60% reduction in iron absorption. Further, cow's milk is low in iron that is poorly absorbed and can result in occult blood loss which can be nutritionally significant<sup>37, 38 39, 40</sup>. Jiang et al., found that children 9.5 months old who were fed cow's milk experienced blood loss that had an adverse effect on iron nutritional status. Although no infant developed iron deficiency or anemia there was a significant decrease in plasma ferritin for children fed cow's milk<sup>38</sup>. The gastrointestinal tracts of younger infants are more responsive to cow's milk but by 12 months the response disappears and iron nutritional status is not affected<sup>40</sup>. If the children in the sample were consuming cow's milk with high frequency for an extended period this may have compromised their iron status.

Finally, an interesting finding was that hemoglobin levels were strongly associated with mothers' perception of their children's level of playfulness and appetite. The more negative the mothers' assessments of their children's behaviors the lower the associated mean hemoglobin levels of the children. This result is striking given that these associations are based on simple questions to the mothers which required the mothers' subjective assessments. However, the results support the assumption that the anemia in the sample of children was biologically significant and had a remarkable impact on child behavior.

This analysis provided a view of the determinants of anemia and hemoglobin levels at one point in time of a group of children 6 to 36 months in the Naryn oblast of Kyrgyzstan. Ideally, to enhance the understanding of the problem of anemia in preschoolers in the Kyrgyz Republic, more detailed studies need to be conducted in different oblasts. These studies should focus on the quantity and quality of the children's diets and feeding behaviors of mothers over an extended period of time. However, although more detailed studies at the oblast levels would be helpful this

analysis provided important insight into the determinants of anemia in Kyrgyz children.

Although anemia is an important problem in Kyrgyzstan it is only one among the many challenges the country has faced since the early nineties. Presently, with over  $\frac{3}{4}$  of the population still impoverished and deterioration in access to basic public services such as education and health the country still faces a myriad of challenges. With the limited resources of a low income country, inefficient health services and a high percentage of the population who are poor, solutions to the problem of anemia will work best in Kyrgyzstan if they are cost-effective and work within the local cultural environment.

In sum, the prevalence of anemia among 6 to 36 month old children is still a significant public health problem for Kyrgyzstan. Significant predictors of anemia were age, intake of meat, breast-milk, fruit and biscuits. Anemia risk was highest among younger children below 24 months. Breast milk was consumed by a small percentage, intake decreased across age groups and cow's milk was used as a substitute for breast milk. Meat, an adequate source of bio-available iron, was accessible to 6 to 12 month old children in the sample but was perhaps not fed in adequate amounts since there was still a high prevalence of anemia among those fed meat. Children in this sample were also given iron inhibiting foods such as cow's milk in large quantities that could have had a negative impact on iron status starting between 6 and 12 months. Further studies are needed to assess the quantity and quality of the iron bio-available or iron inhibiting foods children are fed to further understand their impact on the iron status of Kyrgyz preschoolers.

### ***3.5 CONCLUSIONS***

Anemia was identified as a public health problem in the Central Asian Republics and Kazakhstan initially in the mid-nineties. Based on the results of this

analysis anemia continues to have a presence in Kyrgyzstan among children 6 to 36 months old. Strategies to address anemia where prevalence among 6 to 24 month old children is high and ready access to fortified complementary foods is low should include routine iron supplementation from the first year of life into the second <sup>39</sup>.

In addition to anemia reduction, anemia prevention strategies in Kyrgyzstan must be based on updated, science-based guidelines. In 2003 the WHO published guidelines for feeding of young infants and children which included the Central Asian Republics<sup>33</sup>. These evidence-based guidelines are meant to revise the outdated former Soviet recommendations and address the region's traditional dietary practices that have had adverse affects on nutritional status and particularly iron status. These guidelines can serve as a starting point for the development of national guidelines in each of the CARK for the appropriate feeding of infants and children. If effectively disseminated to health professionals involved in nutrition actions and education that impact the nutritional status of infants and young children, these recommendations will serve to not only serve to assist in the control and prevention of anemia in pre-school children but will also benefit the overall health of young infants and children in the central Asian republics and Kazakhstan.

## REFERENCES

1. Stoltzfus RJ, Mullany L, Black RE. Iron Deficiency Anemia. In: Ezzati, M, Lopez, AD, Rodgers, A and Murray, CJL, eds. In Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors. Geneva: World Health Organization, 2004.
2. Kraemer K. ed. Nutritional Anemia. Zurich, Switzerland: Sight and Life Press, 2007.
3. Gera T, Sachdev HP, Nestel P, Sachdev SS. Effect of iron supplementation on haemoglobin response in children: systematic review of randomized controlled trials. *J Pediatr Gastroenterol Nutr* 2007;44:468-86.
4. Baker SJ, DeMaeyer EM. Nutritional anemia: its understanding and control with special reference to the work of the World Health Organization. *Am J Clin Nutr* 1979;32: 368-417.
5. Brown KH. Breastfeeding and complementary feeding of children up to 2 years of age. *Nestle Nutr Workshop Ser Pediatr Program* 2007;60:1,10; discussion 10-3.
6. Dewey KG. Nutrition, growth, and complementary feeding of the breastfed infant. *Pediatr Clin North Am* 2001;48:87-104.
7. Stoltzfus RJ, Heidkamp R, Kenkel D, Habicht JP. Iron supplementation of young children: learning from the new evidence. *Food Nutr Bull* 2007;28: 4.Suppl: S572-84.
8. Lozoff B, Klein NK, Nelson EC, McClish DK, Manuel M, Chacon ME. Behavior of infants with iron-deficiency anemia. *Child Dev* 1998;69:24-36.

9. Dallman PR, Siimes MA, Stekel A. Iron deficiency in infancy and childhood. *Am J Clin Nutr* 1980;33:86-118.
10. Sharmanov A. Anaemia in Central Asia: demographic and health survey experience. *Food and Nutr Bull* 1998;19:307-17.
11. Darnton-Hill I. Anaemia prevention and control mid-term evaluation for UNICEF-CARK regional office central Asia republics and Kazakhstan. New York: Human Nutrition Institute, Columbia University, 2002.
12. Gleason GR, Sharmanov T. Anemia prevention and control in four central Asian republics and Kazakhstan.; *J Nutr* 2002;132:
13. Anonymous. Kyrgyz Republic 1997: results from the Demographic and Health Survey. *Stud Fam Plann* 1999;30:347-51.
14. Scrimshaw N. Frequency, cause and significance of iron deficiency for the children of Central Asia. *J Child Health* 1998;9:47.
15. Schuth T. Kyrgyz-Swiss health reform support project phase III annual report 2005. Bishkek Kyrgyzstan: Swiss Red Cross, 2006.
16. Tazhibayev S, Dolmatova O, Ganiyeva G, et al. Sentinel Study Evaluation of the Potential Effectiveness of Wheat Flour and Salt Fortification Programs in Five Central Asian Countries and Mongolia, 2002-2007. In Press 2008.
17. Frisancho AR. Human Adaptation to High-Altitude Environments. In: Anonymous Humankind Evolving: An Exploration of the Origins of Human Diversity. Dubuque, Iowa: Kendall/Hunt, 2006:301.



18. Dirren H, Logman MH, Barclay DV, Freire WB. Altitude correction for hemoglobin. *Eur J of Clin Nutr* 1994;48:625-32.
19. Cohen JH, Haas JD. Hemoglobin correction factors for estimating the prevalence of iron deficiency anemia in pregnant women residing at high altitudes in Bolivia. *Rev Panam Salud Publica* 1999;6:392-9.
20. Beall CM. Two routes to functional adaptation: Tibetan and Andean high-altitude natives. *Proc Nat Acad Sci USA* 2007;104 Suppl 1:8655-60.
21. WHO (1968). *Nutritional Anaemias*. WHO Technical Report Series No. 405, World Health Organization, Geneva, Switzerland .
22. Bhutta ZA, Ahmed T, Black RE, et al. What works? Interventions for maternal and child undernutrition and survival. *Lancet* 2008; 371:417-40.
23. Dewey KG. *Guiding Principles for Complementary Feeding of the Breastfed child*. Washington, D.C.: Pan Am Health Org, 2001.
24. Dewey KG, Cohen RJ, Brown KH. Exclusive breast-feeding for 6 months, with iron supplementation, maintains adequate micronutrient status among term, low-birthweight, breast-fed infants in Honduras. *J Nutr* 2004;134:1091-8.
25. Kramer MS, Kakuma R. The optimal duration of exclusive breastfeeding: a systematic review. *Adv Exp Med Biol* 2004;554:63-77.
26. Brown KH, Dewey KG, Allen L, Saadeh RJ, Programme of Nutrition. *Complementary feeding of young children in developing countries : a review of current scientific knowledge*. WHO/NUT/98:1 ed. Geneva: World Health Organization, 1998.

27. Gibson RS, Ferguson EL, Lehrfeld J. Complementary foods for infant feeding in developing countries: their nutrient adequacy and improvement. *Eur J Clin Nutr* 1998;52:764-70.
28. Gibson RS, Hotz C. The adequacy of micronutrients in complementary foods. *Pediatrics* 2000;106:1298-9.
29. Lutter CK, Dewey KG. Proposed nutrient composition for fortified complementary foods. *J Nutr* 2003;133:3011S-20S.
30. Nestel, P. and Davidsson, L. Anemia, Iron Deficiency and Iron Deficiency Anemia. Washington DC: INACG, 2002.
31. Krebs NF. Meat as an early complementary food for infants: implications for macro- and micronutrient intakes. *Nestle Nutr Workshop Ser Pediatr Program* 2007;60:221,9; discussion 229-33.
32. Krebs NF. Food choices to meet nutritional needs of breast-fed infants and toddlers on mixed diets. *J Nutr* 2007;137:511S-7S.
33. World Health Organization (WHO). Feeding and nutrition of infants and young children. Guidelines for the WHO European region, with emphasis on the former Soviet countries. Copenhagen: WHO Regional Office for Europe, 2000b.
34. Hallberg L, Brune M, Erlandsson M, Sandberg AS, Rossander-Hultén L. Calcium: effect of different amounts on nonheme- and heme-iron absorption in humans. *Am J Clin Nutr* 1991;53:112-9.
35. Roughead ZK, Zito CA, Hunt JR. Inhibitory effects of dietary calcium on the initial uptake and subsequent retention of heme and nonheme iron in humans: comparisons using an intestinal lavage method. *Am J Clin Nutr* 2005;82:589-97.

36. World Health Organization (WHO). Complementary Feeding and the Control of Iron Deficiency Anaemia in the Newly Independent States. Copenhagen: WHO Regional Office for Europe, 2000.
37. Jiang Q, Huang XJ, Chen H, et al. Severe gastrointestinal bleeding after allogeneic hematopoietic stem cell transplantation--15 case analysis. *Zhonghua Xue Ye Xue Za Zhi* 2005;26:277-80.
38. Jiang T, Jeter JM, Nelson SE, Ziegler EE. Intestinal blood loss during cow milk feeding in older infants: quantitative measurements. *Arch Pediatr Adolesc Med* 2000;154:673-8.
39. Ziegler EE, Fomon SJ, Nelson SE, et al. Cow milk feeding in infancy: further observations on blood loss from the gastrointestinal tract. *J Pediatr* 1990;116:11-8.
40. Ziegler EE, Jiang T, Romero E, Vinco A, Frantz JA, Nelson SE. Cow's milk and intestinal blood loss in late infancy. *J Pediatr* 1999; 135:720-6.
41. Zlotkin S, Arthur P, Schauer C, Antwi KY, Yeung G, Piekarz A. Home-fortification with iron and zinc sprinkles or iron sprinkles alone successfully treats anemia in infants and young children. *J Nutr* 2003; 133:1075-80.
42. Nestel P. Adjusting Hemoglobin Values in Program Surveys. International Nutritional Anemia Consultative Group, Washington, D.C., 2002.
43. Library of Congress- Federal Research Division. Country Profile : Kyrgyzstan, November 2005.
44. Anderson J. Kyrgyzstan: Central Asia's Island of Democracy? Australia: Hardwood Academic Publishers, 1999.
45. Everett-Heath T. ed. Central Asia: Aspects of Transition. New York: Routledge, 2003.

46. Bauer A, Boschmann N, Green, DJ and Kuehnast K. A Generation at Risk: Children in the Central Asian Republics of Kazakhstan and Kyrgyzstan. Manila: Asian Development Bank (ADB), 1998.

47. Mambetov M. European Observatory on Health Care Systems. Health Care Systems in Transition: Kyrgyzstan. Ministry of Health Kyrgyzstan 2005.

48. International Monetary Fund and the International Development Association Kyrgyz Republic: Joint Staff Assessment of the Poverty Reduction Strategy Paper. Annual Progress Report. 2004.

49. Research Institute of Obstetrics and Pediatrics [Kyrgyz Republic] and Macro International Inc. 1998. Kyrgyz Republic Demographic and Health Survey, 1997. Calverton, Maryland: Research Institute of Obstetrics and Pediatrics, Ministry of Health of the Kyrgyz Republic and Macro International Inc.

50. Yang Z, Lönnerdal B, Adu-Afarwuah S, Brown KH, Chaparro CM, Cohen RJ, Domellöf M, Hernell O, Lartey A, Dewey KG. Prevalence and predictors of iron deficiency in fully breastfed infants at 6 mo of age: comparison of data from 6 studies. Am J Clin Nutr. 2009;89:1433-40.

## CHAPTER 4

### COSTS AND COST-EFFECTIVENESS OF SPRINKLES TO REDUCE OR PREVENT ANEMIA IN PRESCHOOL CHILDREN

#### **4.1 BACKGROUND**

In resource-poor nations of Africa and Asia, iron deficiency anemia (IDA) is a highly prevalent and unrelenting nutritional problem for pre-school children<sup>1</sup>. Bridging the gap between iron taken in and absorbed and iron requirements by providing preschoolers with supplemental iron to ensure proper physical and cognitive development<sup>1,2</sup> would be a crucial step toward eliminating IDA in infants and children in developing countries.

There is an urgent need for low cost methods that are effective in delivering iron to infants and young children in the form of fortified complementary foods or supplements<sup>2-5</sup>. Food fortification and iron supplementation, the two methods currently used to address IDA in preschool aged children in developing countries have had limited success<sup>6-7</sup>. In developing countries, fortification is often centralized and the poorest and most vulnerable continue to use local, cereal-based, unfortified complementary foods<sup>8-10</sup>. Iron supplementation has improved the iron status of infants and children in efficacy trials<sup>10-13</sup>. However, in the context of large-scaled supplementation programs, low compliance and coverage have reduced effectiveness of supplementation<sup>9, 14</sup>. Given the persistence of IDA in infants and children over the past few decades and the limitations of fortification and supplementation, the need for new, cost-effective strategies proven to reduce IDA in infants and children is urgent.

##### **4.1.1 Sprinkles**

Innovative approaches to overcoming barriers to iron supplementation and enhancing the intake of bio-available iron are needed to address the problem of IDA. One new

approach is Sprinkles; ferrous fumarate microencapsulated in a soya-based hydrogenated lipid that has been introduced as a home-based fortification approach to anemia reduction<sup>15</sup>. Sprinkles have proved efficacious, in treating and preventing IDA in young infants and children<sup>15-18</sup>. Currently, Sprinkles are being distributed in large-scale nutrition programs with different populations groups such as Canadian First nation and Inuit<sup>19</sup> Indonesians<sup>20</sup>, Cambodians<sup>21</sup>, Haitians<sup>22</sup> and Mongolians<sup>23</sup>, and are scheduled to be used in other nutrition programs world-wide. To understand the potential of Sprinkles to impact the problem of IDA in children, it is important to look beyond efficacy and evaluate the cost-effectiveness of this new method.

#### ***4.1.2 Objective***

The objective of the present study was to evaluate the cost-effectiveness of Sprinkles in reducing or preventing anemia in infants and young children. Our analysis is conducted in three phases. First, we conduct a cost analysis describing the costs of the Sprinkles intervention. Because the costs to reduce anemia stem from both the cost of iron supplements as well as the system that is used to deliver them, an attempt was made, throughout the analysis, to distinguish those costs associated with the delivery system from those associated with the supplementation program itself. Cost associated with the delivery system includes those which ensure supply, delivery and consumption of supplements. Costing the delivery system separately was intended to improve the external validity of this study. Programs with a different structure or system of delivery than the program presented in this analysis may then find utility in the information provided in this analysis beyond the final cost-effectiveness ratios (CERs).

Next, we conduct an analysis of the impact of Sprinkles on anemia in a group of preschool children. Finally, using the cost and impact results we calculate cost-

effectiveness ratios in terms of cost per child per 1g/L change in hemoglobin. To our knowledge the cost-effectiveness of Sprinkles in a programmatic setting has not yet been assessed.

#### ***4.1.3 Audience***

This study will provide information for those responsible for prioritizing and allocating funds for the implementation of Sprinkles interventions. Conclusions drawn from this analysis will provide decision makers with critical information regarding the adoption of this new method relative to existing methods used to treat anemia. The intended audience includes country-specific government agencies non-governmental organizations and program managers considering providing Sprinkles for preschool children.

#### ***4.1.4 Analytical Method***

Three of the main types of efficiency assessments used to evaluate the costs and health effects of specific interventions in public health are cost-benefit analysis (CBA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA)<sup>24,25</sup>. CBAs are a form of analysis that present the final comparison of costs and benefits in a common metric (often monetary). These allow for easy comparison across a wide variety of programs however, the monetary valuation of qualitative benefits is difficult and raises controversial questions<sup>24,25</sup>. On the other hand, during a CEA and CUA no monetary value is assigned to the final health outcome. Instead, outcomes are measured in standard health units. In the CEA the unit of measure depends on the outcome that is most relevant to the analysis and the net cost of implementing a particular strategy is related to the effectiveness of the intervention. Although the CEA is limited in its use for comparison across studies with results of different health conditions, it is useful when selecting the most cost-effective strategies from a set of

interventions with a common outcome. Further, a CEA does not include judgments regarding the value and quality of lives beyond a person's economic contribution. This assessment is left to the user of the study results<sup>24,25</sup>.

A CUA, a specific type of CEA, explicitly includes judgments on the value of quality of life in the calculation. The common measure is the quality-adjusted life years (QALYs) and final outcomes are expressed as the number of life years saved, with a quality of life adjustment. All three economic models can be used to directly link interventions to a health outcome of interest and eventually guide how program resources are allocated, however, the method of analysis chosen must take into account the study's target audience, the availability of data and the study question being addressed<sup>25</sup>.

The target audiences for this study are those in program settings that must decide how much the cost would be, per child, to use Sprinkles to raise the hemoglobin levels of infants and young children in comparison to other iron supplementation methods. Therefore, to make our study more relevant to the context in which our target audience operates, we conduct a CEA and present our results as a ratio of costs per child per 1 g/L change in hemoglobin. This will not only assist in informing our target audience but also provide a means of relating Sprinkles impact (mean changes in hemoglobin levels) across different populations with different levels of anemia.

A CEA was found more suitable for this analysis than a CUA given the focus on the impact of Sprinkles on increasing hemoglobin levels and reducing the prevalence of anemia in childhood (among children 6 to 36 months old). The world health organization (WHO) recommends that the effectiveness of each strategy be expressed as years of life lost (YLLs) and disability adjusted life years (DALYs) to allow for comparability across interventions<sup>26, 27</sup>. However, calculating these



outcomes can be more scientifically supported when anemia is linked to perinatal mortality<sup>28</sup>. Given that the data available for this analysis were collected on children 6 to 36 months , going beyond a CEA to conduct a CUA to calculate DALYs gained for pre-school children supplemented with iron would require assumptions regarding the link between anemia and childhood mortality that are not currently supported by the literature<sup>28</sup>.

Attempting to monetize the benefits that are produced (CBA) or extending the results of the immediate impact of Sprinkles on childhood anemia to make a statement about future benefits (CUA) goes beyond the objective of this analysis. In addition, there will be no attempt made to estimate the changes in health and non-health consumption as a result of the improvements in hemoglobin (Hb) levels resulting from the Sprinkles intervention.

Sensitivity analyses will be conducted exploring the uncertainties associated with the estimates of costs and effects. Defining the profile of the null was done using a natural history model where data were used (from a control group) that describe the natural incidence rates/prevalence of the disease without treatment.

#### ***4.1.5 Time Frame and Analytical Horizon***

This study assesses the cost-effectiveness of using Sprinkles to prevent or treat anemia over a period of 6 months. No attempts were made to assess the future benefits associated with each case of anemia prevented beyond the period of the intervention.

#### ***4.1.6 Future Costs and Benefits***

Although the program was 6 months in duration (between November 2005 to April 2006), costs and benefits were collected for all activities related to the program which included planning activities that began in March 2005. Because all costs were

incurred within a year we do not discount and treat everything as current costs for the year 2005.

#### ***4.1.7 Analytical Perspective***

Typically prevention-effectiveness studies adapt a societal perspective which includes all costs and all benefits of the program whether incurred by the program provider (regardless of who pays) or participant (regardless of who receives services)<sup>25</sup>. In this analysis, because the results were intended to inform decision makers regarding a specific intervention program, a narrower perspective was also be included that takes into account the budgetary concerns of program decision-makers regarding Sprinkles intervention.

### ***4.2 DATA AND METHODS***

#### ***4.2.1 Study Context and Population:***

##### ***4.2.1.1 The KSHRSP***

Since the year 2000, the Kyrgyz-Swiss Health Reform Support Project (KSHRSP) has been integral in supporting health reform developed by the Kyrgyz Ministry of Health (MOH) with the support of the World Health Organization (WHO) and the World Bank (WB). The KSHRSP was implemented in 3 phases beginning in 2000. The objectives of Phases I and II were to improve infrastructure of essential medical facilities in Naryn oblast<sup>20</sup>; support the restructuring of the health care system in Naryn according to the health reform and strengthen public health and primary health care in the Naryn oblast.

During these phases, the community action for health (CAH) was introduced as a model of health promotion in which village health committees (VHC) members

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<sup>20</sup> An oblast is similar to a province or a state

were elected by the community to analyze and prioritize their health issues. In partnership with the community primary health care units (PHC) the VHC members plan and coordinate and carry out actions to address village health issues. Other health actions initiated were at the hospital level and focused on hospital hygiene. Phases III and IV (from 2004 to 2008) extended actions of infrastructure investments and public health reform into other oblasts.

#### *4.2. 1.2 Kyrgyz Health Service Structure*

The KSHRSP Sprinkles intervention was closely linked with the Kyrgyz MOH services. In order to understand how the Sprinkles intervention costs were assessed, it is important to first understand how the Kyrgyz health services are structured. The Soviets established a network of health care<sup>26</sup> facilities at the village, district/regional and national levels. Although the Kyrgyz MANAS health reform is currently underway, health care services are still delivered through a hierarchy of services as during the Soviet period. Nationally, the MOH supervises the training and research activities that occur in all Kyrgyz health institutions. At the regional level primary and secondary health care are administered through polyclinics and district hospitals. A district hospital or family medical center (FMC), located in the central town of each district (raion), is headed by a chief physician appointed by the oblast administration. The chief physician is charged with the direction of the local primary and secondary health care services.

Primary health care<sup>21</sup> contacts for the population are primary health units (PHUs) such as feldsher-midwifery posts (FAPs), physician clinics (SVA) and rural health centers (in rural areas such as villages and small towns respectively) and

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<sup>21</sup> In Kyrgyzstan, Primary health care includes general medical care as well as health promotion and disease prevention and for the majority refers to the first point of contact for the population with the health care system (EOHCS, 2000).

polyclinics in urban areas. At the village level, FAPs (small health posts) are staffed by a feldsher (a midwife or nurse providing services to a rural population catchment area of 500-2000). FAPs provide basic care; dispense and prescribe medications; as well as conduct health prevention and education activities. SVAs serve a population of 6000-10,000 and are staffed with physicians (including dentists). Polyclinics, staffed by medical specialists, serve populations living in towns and cities and referred patients from rural areas. These polyclinics can be located in the central district hospitals (as in the case in the raion centre) or can be free-standing. Family group practices (FGPs) were a health model introduced in 1995 and have only rolled out in some oblasts. In rural areas, FGPs are restructured SVAs and FAPs. These health centers consist of internists, pediatricians, and obstetrician/gynecologists along with nurses.

In phase II of its implementation the CAH model was integrated into the Kyrgyz health care system. As a part of the integration of CAH into the health system, VHCs collaborate closely with FGPs/FAPs and health promotion units (HPU) located in the FMCs. The Sprinkles intervention was conducted within the context of the KSHRSP's CAH program.

#### *4.2.1.3 KSHRSP Sprinkles Program*

The KSHRSP Sprinkles program was implemented between November 3, 2005 and April 30, 2006. Sprinkles were distributed in one raion of the Nayrn oblast, At-Bashy, with a population of 50,000. Target groups for the Sprinkles intervention were all eligible children aged 6-36 months and 7-16 weeks pregnant and lactating women residing in At-Bashy. Sprinkles were distributed to 4300 children, 1300 pregnant and 1300 lactating women. This analysis focused only on children aged 6 to 36 months.

### *Sprinkles Dosage*

The Sprinkles dosage level for children was a weekly administration of 30 mg of iron as ferrous fumarate. Each sachet also contained 300 µg of vitamin A (retinol acetate USP), 5 mg of zinc (zinc gluconate USP), 30 mg of vitamin C (ascorbic acid USP-FCC) and 160 µg of folic acid (folic acid USP).

### *Distribution and Monitoring*

Sprinkles were distributed to the households of all children participating in the intervention by the MOH staff and the VHC members in charge of anemia prevention. Each participant received a plastic bag with 24 Sprinkles packages and 6 extra in case of loss. They received their entire 6 month allotment of Sprinkles and an information list detailing how to take Sprinkles. Mothers were instructed to give their children 1 sachet of Sprinkles weekly, every Thursday for 6 months beginning on November 3, 2005, and to cross the date off the information list when the child was given Sprinkles. Mothers were shown how to fill out the information list and after signing a consent form they received their quota of Sprinkles in a bag that was hung on the wall in their homes by a tack. Sprinkles intake was controlled by mothers but after the initial distribution MOH and VHC members reported making unscheduled visits to different households to promote and monitor compliance.

## ***4.2.2 Data collection***

### *4.2.2.1 Effectiveness*

### *Study Design and Sample*

To evaluate the effectiveness of the program, a sample of children were randomly selected. Study participants receiving the intervention were in At-Bashy

and those selected from Kochkor and Naryn raions served as controls. Two different groups of children, aged 6-36 months, were selected prior to (pre-intervention) and at 6 months after Sprinkles distribution (post-intervention), and their hemoglobin (Hb) levels measured. One drop of blood from a heel-prick was collected in a HemoCue microcuvette, from each participant, and hemoglobin concentration was read directly in the field. No other indicators for iron status were assessed.

In addition to blood samples, socio-demographic and dietary information were collected via a questionnaire. Socio-demographic questions included information on the age and sex of the child, the child's family size, level of education attained by the child's mother, meat consumption by the child's mother and household ownership of land and livestock. In addition, dietary information was collected based on mothers' recall of whether or not a child was given a certain food item in the 24 hours prior to being surveyed. Additional questions related to the child's level of playfulness and appetite, whether the child had received iron or vitamin A supplements in the months prior to the survey were also included.

In the two control raions Kochkor and Naryn, 314 children randomly selected had their Hb levels measured and their mothers were asked to complete a questionnaire in tandem with the At-Bashy assessment timeline.

### Program Impact

The program impact was estimated using double difference regression estimates which compared the differences from pre- to -post- intervention in the treatment versus control areas. The regression equation used to estimate this was:

$$Hb_{it} = \beta_0 + \beta_1 T_i + \beta_2 AFT_i + \beta_3 T_i * AFT_i + \sum \beta_i X_{jit} + e_{it}$$

Where  $Hb_{it}$  is the  $i$ th child's hemoglobin level in time period  $t$  (before or after intervention),  $TRT$  is a binary variable which is 1 if the child lives in the treatment

community and 0 otherwise,  $AFT$  is 1 if Hb was measured after the intervention and 0 if before. And  $X_{jit}$  represents the vector of  $J$  control variables for individual  $i$ , in time  $t$ . These variables include the child's age and sex; mother's education level and meat intake; household's family size; ownership of land, sheep/goat and cows/horses. The coefficient  $\beta_3$  measures the double difference treatment effect.

Anemia was defined as Hb less than 110 g/L. To incorporate the evidence of the program impact (effectiveness) into the cost-effectiveness ratio, the impact was measured in terms of the number of grams/Liter change in hemoglobin per child between pre-and post intervention.

#### *4.2.2.2 Costs*

##### *Cost Collection*

The approach of this cost analysis was to identify the total cost of the resources and efforts used to implement the KSHRSP Sprinkles intervention program. All costs relevant to implementation of the KSHRSP Sprinkles intervention were identified and assessed retrospectively in July 2006, three months after the intervention was scheduled to end. To estimate costs, we interviewed key informants who included a selection of KSHRSP staff, ministry of health staff, VHC members and mothers who were involved in the intervention.

An ingredients approach was used and the cost inventory developed was inclusive of all costs necessary for implementation. The cost list, in the Appendix, was used as a guide during data collection so that all potential costs were captured. Only financial and economic costs, relevant to the implementation of the Sprinkles intervention were considered when calculating total cost. The project's capital costs, such as the cost related to the KSHRSP facilities in Bishkek (i.e. office rent,

maintenance) were considered not to change incrementally based on the addition of the Sprinkles intervention and were therefore not included in this analysis.

Costs were assessed for the planning and implementation of activities of the KSHRSP Sprinkles distribution program for all children between the ages of 6 to 36 months residing in At-Bashy raion in November 2005. The planning period for the intervention ran from March to October 2005. Although Sprinkles distribution was planned for 4300 children, 1300 pregnant and 1300 lactating women this analysis is only concerned with the effect and cost of Sprinkles on anemia in children.

Throughout this analysis, we assumed that distribution of Sprinkles to the children alone drew on 62% of the total implementation activity efforts and costs were adjusted accordingly. Sixty-two percent was selected based on the assumption that 62% of the costs of the intervention activities could be attributed to distribution to children alone. This was based on the ratio of the number of children to the number of women who received Sprinkles assuming that each household that had children had no other recipients of Sprinkles.

In order to disaggregate intervention costs we differentiated according to the natural sequence of activities from the planning of the intervention to the distribution of Sprinkles. These activities were: planning, training, evaluations, distribution and monitoring. A list of these activities and associated financial and economic costs are presented in Table 4.1. The evaluation component of the intervention was not included in the final costs since the program could have been conducted without these activities. For each activity, costs were assessed by taking into account the opportunity cost of all programme inputs. These included valuing the labor of paid (reported monthly salary for KSHRSP and MOH employees and percentage time contribution to



the activity) and unpaid labor (for unpaid labor, the Kyrgyz average minimum monthly wage of \$46.40 for 2005 was used<sup>22</sup>) materials used and travel time spent.

### Cost Analysis

#### ***Planning/Preparation***

The major planning activities for the KSHRSP Sprinkles intervention took place in the capital city of Bishkek at the KSHRSP headquarters from March 2005 to June 2005. This phase began with planning meetings between the KSHRSP staff member who was directly responsible for the Sprinkles project : the coordinator of quality improvement and research and the team leader. Planning activities included, developing consent forms, sorting and packaging of sprinkles, preparing leaflets for participants and obtaining consent to use Sprinkles in Kyrgyzstan from the Kyrgyz pharmacological committee. Other activities were identifying and hiring requisite personnel, developing training manuals and carrying out trainings.

From March 2005 until June 2005 the cost related to the coordinator of quality improvement's contribution was equivalent to his salary of \$500/ month at 80% of his time contributed to Sprinkles  $(500 \times 0.80) \times 4 \text{ months} = \$1000$ . Here we also consider the coordinator of quality improvement's time from July 2005 until April 2006 the value of the coordinator of quality improvement's time was 10 months  $\times$  50% of work time  $(\$500 \times 0.5) = \$2500$ . Total time for the coordinator of quality improvement in all phases of the intervention was valued at \$3500. Sixty-two percent of this cost was attributed to the distribution to children alone. The total value of the coordinator of quality improvement's time was \$2170.00.

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<sup>22</sup> Library of Congress 2006.

**Table 4.1:** Intervention Activities and Costs

<b>Planning/Preparation</b>	<b>Costs</b>
<b>Planning meetings/Strategic Plan development</b>	
CQI March- June 2005	\$620.00
CQI July 2005-April 2006	\$1,550.00
Team Leader 2 weeks	\$930.00
Team Leader 13.5 months	\$3,515.40
Health Promotion Coordinator	\$828.00
Research Team Time for training and Sprinkles	
Registration	\$1,183.22
Sprinkles Registration Fee	\$465.00
Training Manual Production	\$263.50
3 trainers per diem	\$45.31
Purchasing/Ordering/Shipment/Receipt of Sprinkles	\$14,976.03
Sorting/Packaging Sprinkles	\$231.61
Plastic sachets to hold Sprinkles	\$53.39
Meals during sorting	\$25.96
Stationary/photocopying	\$505.63
Artist to develop leaflet pictures	\$31.00
Document translations	\$448.26
Purchase of Hemocue machines/accessories	\$491.67
<b>Trainings</b>	
#1-Training of At-Bashy senior medical Staff	
Health Promotion Specialist	\$21.56
Nurse	\$23.86
#2-Training of FAP/FGP/FMC	\$46.08
#3 -Training of VHCs	\$54.80
#4 -Distribution Training	\$70.44
Trainer	\$22.49
CQI Per diem Sept-April	\$25.89
HPS October-December 2005	\$73.00
HPS Jan-April 2006	\$67.77
<b>Surveys</b>	
<b>Research Team Survey Activities</b>	
Baseline	\$816.29
3 months	\$1,550.31
6 months	\$1,773.91
Mothers time during survey	\$59.89
Distributing Sprinkles	\$506.48

**Table 4.1 (Continued)**

Mothers time during distribution	\$415.67
<b>Monitoring/Supervision</b>	
HPU monitoring visit	\$48.64
Monitoring visits VHCs FGP/FAP members	\$2,723.78
VHC bi-monthly meetings	\$256.75
Quarterly monitoring meetings	\$11.43
Monthly monitoring meetings	\$70.16
Mother's time during monitoring	\$2,222.33
<b>Travel</b>	
HPU travel time for monitoring visit	\$18.50
Travel time and cost for quarterly meeting	\$90.93
Travel time for Monitoring meetings VHCs and FGP/FAPs	\$576.67
KSHRSP transportation costs	\$1,567.78
KSHRSP accomodation costs	\$428.62

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CQI= Coordinator of Quality Improvement; FAP= Family Accoucher  
Point  
Red Cross

Several meetings took place between the coordinator of quality improvement and the team leader 5 days per week for 2 hours for 2 weeks. A total of  $(10 \times 2 = 20)$  20 hours of time. During this period the team leader's time is valued at \$150/day salary  $\times 10 \text{ days} \times 62\% = \$930.00$ . For the remaining 13.5 months the team leader contributed 10 % of his time which has a value of  $\$5670.00 \times 62\% = \$3515.40$ .

In addition to the coordinator of quality improvement the KSHRSP health promotion coordinator and 3 trainers, based in the Naryn oblast, were involved in the planning phases. Their level of contributions varied. During the planning period the health promotion coordinator contributed time to work on the selection of a research team as well as developing the protocol for testing of Sprinkles. The health promotion coordinator also contributed by providing technical support as needed throughout the project. The health promotion coordinator received a monthly salary of \$600.00 per month. Estimated time spent on the project was 100% for 1 month during planning activities and then 10% per month during the remaining months of the intervention. The total estimate of the health promotion coordinator's contribution for one year is  $\$600 + \$780 = \$1380.00 \times 62\% = \$828.00$ .

The trainers involved assisted in the development of a training manual which outlined the strategy for presenting Sprinkles to the local health personnel as well as the VHCs. This was developed over a period of 2 weeks with the coordinator of quality improvement during the planning period. Their average salaries are \$250, \$250 and \$350 per month respectively. The trainers were based in Naryn and would have received per diem for the 2 weeks they were in Bishkek. For half the month the total for the contribution of the trainers was  $\$425.00 \times 62\% = \$263.50$ . For per diem, KSHRSP employees per diem is 70 soms per day = \$1.74. For 14 days the 3 trainers

would have received  $14 \times 3 \times \$1.74 = \$73.08$ . The value of the trainers for the development of the training manual was  $\$73.08 \times 62\% = 45.31 + \$263.50 = \$308.81$ .

### **Sprinkles Approval**

Sprinkles were a new product in Kyrgyzstan and needed to undergo an approval process. The coordinator of quality improvement and the team leader worked with a research team to develop a clinical testing program that would define the basis for how Sprinkles would be used in the country. The research team was a group of 6 Kyrgyz physicians. Approval to use Sprinkles was obtained from the MOH's pharmacological committee, department of supplements and medical techniques. The KSHRSP paid \$750.00 for the registration of Sprinkles. Other costs relating to registration activity involved the testing that was carried out by the research team during the planning period. Their reimbursement for this period was \$1908.42. Total cost for the registration for Sprinkles for clinical testing was  $\$750 + \$1908.42 = \$2658.42$  and for the child participants alone it was \$1648.22.

### **Cost of Sprinkles**

Each sachet of Sprinkles for this age group costs the KSHRSP \$0.10<sup>23</sup>. Each child was provided with 1 sachet per week for 24 weeks with an additional 6 sachets for losses. Given that this analysis will focus on children 6 to 36 months, only the costs of purchasing Sprinkles for this age group were calculated.

The KSHRSP ordered 250,000 sachets from the Sprinkles Global Health Initiative in Canada (150,000 for children and 100,000 for women). The total number of sachets needed for 4300 children for the entire intervention was 12,900 which

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<sup>23</sup> Sprinkles were developed in Canada by the Sprinkles Global Health Initiative at a cost of \$0.015 per sachet. The Sprinkles the KSHRSP used were ordered in Canada and exported to Kyrgyzstan and therefore cost more per sachet than if they were produced locally.

would cost \$12,900.00. To account for extra costs associated with the purchase of Sprinkles, we used the total amount paid for all of the KSHRSP ordered: \$21,300.00. The direct cost of the Sprinkles (\$0.10 per sachet for children and \$0.025 per woman's sachet) would be  $\$15,000.00 + \$2,500.00 = \$17,500.00$ . The extra cost of Sprinkles was calculated by subtracting the amount KSHRSP paid for the delivered Sprinkles from the cost of Sprinkles. The difference was  $\$21,300 - \$17,500 = \$3,800.00$ . We assumed that this is the total extra cost for ordering Sprinkles which includes all processing and shipping required to transport the Sprinkles from Canada to the KSHRSP office in Kyrgyzstan. The extra cost per Sprinkles ordered was  $\$3,800/250,000 = \$0.0152$ . The total extra cost for the 4300 packets ordered for the children was  $\$1960.80$ . Therefore the total cost of Sprinkles for the children is  $\$12,900.00 + \$1960.80 = \$14,860.80$ . Duties and storage paid for Sprinkles upon arrival in Kyrgyzstan were \$223.32 in total. The portion of this added to the cost of 4300 Sprinkles would be  $(\$223.32/250000) \times 4300 \times 30 = \$115.23$ . The total cost for the purchase and shipping of Sprinkles for 4300 children was \$14,976.03.

### **Preparation of Sprinkles**

After Sprinkles arrived at the KSHRSP office in Bishkek, they were sorted and packaged in plastic sachets for each participant along with an information list and a tack for hanging for each participant. A special storage space was not provided for Sprinkles so will not be accounted for in this analysis. The packaging and sorting was completed in a total of 12 hours by 5 KSHRSP staff members and 7 non-staff members. The 5 staff members were paid for the time spent sorting on the weekend. The other non-staff members were also compensated for their time. KSHRSP staff members were each compensated 1000 soms = \$24.84 using a 2005 exchange rate of 40.25 SOMS. The amount the KSHRSP employees were compensated for sorting was

$\$24.84 \times 5 \text{ staff members} = \$124.20$ . The non-KSHRSP staffs were paid \$249.36. Other expenses related to sorting were meals for the sorters (\$ 41.87) and the plastic sachets used to hold the 24 + 6 Sprinkles for each participant (\$86.12). The total amount for sorting Sprinkles for the child participants was  $(\$124.20 + \$249.36 + \$41.87 + \$86.12) \times 62\% = \$310.96$ .

### **Other items purchased**

In addition to Sprinkles, other items purchased for the monitoring and evaluation of the Sprinkles study were HemoCue machines and micro-cuvettes for assessing blood levels of hemoglobin. The Hemocue cost \$231.99. The cost of accessories such as batteries and was \$222.30 Customs on these items were \$338.72. Total costs for other items were \$793.01. Cost of these items for the 4300 children who received Sprinkles was \$ 491.67.

### **Stationary**

For the preparation and monitoring of the Sprinkles stationary purchases were made. These costs will be addressed here in total and include, photocopying of leaflets as well as questionnaires for surveys ( this was done by an external source), the paper used for photocopying as well as the stationary used in training sessions. The total financial cost was \$815.54. The artist was paid \$50.00 for the development of pictures on the leaflets that accompanied the Sprinkles. Therefore the total cost for preparation of Sprinkles questionnaires and monitoring leaflets for child participants was  $\$865.54 \times 62\% = \$536.63$ .

### **Document Translation**

In preparation for the intervention, documents were translated into Russian as well as the Kyrgyz languages. Translation was done by outside sources. This included translation of documents related to Sprinkles and anemia prevention that were



distributed to the beneficiaries and translations of documents accompanying the Hemocue used to collect blood samples for Hb measurements. The total spent on these translation costs for children was  $\$723.00 \times 62\% = \$448.26$ .

### ***Trainings***

KSHRSP staff was responsible for training the Kyrgyz MOH medical officer in charge of health promotion. The health promotion specialist (HPS) assisted in training other MOH health staff in the FGPs/FAPs as well as the VHCs. Training sessions were efficient in that they were informal and brief. They were often in the form of short meetings with very little training supplies beyond markers and a single sheet of flip-chart paper. The costs of training supplies were negligible and thus they were omitted. Food was provided depending on the length of the meeting. The participants' time was valued using their average monthly salaries. MOH medical staff was reported to be paid between 600 and 3000 SOMS or \$14.91 and \$74.53 based on qualifications (degrees obtained), level of experience and level of responsibility. Where individuals salaries were not reported by medical staff in At-Bashy who participated in the Sprinkles intervention, the average monthly salary used to value time was: for doctors was \$60.00 and for nurses \$37.00, and for hygiene personnel/feldshers \$20.00<sup>24</sup>. The VHC member and mother's times are valued using the 2005 Kyrgyz daily wage of \$2.30<sup>25</sup>.

In 2005 the KSHRSP worked with 17 villages in At-Bashy raion and 17 VHCs in At-Bashy. The HPS reported a total of 238 VHC members and that in smaller villages, there was often 1 person per action group. For this analysis, in the 11 smaller villages that had only FAPs we estimated a total of 55 VHCs: one per action group per

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<sup>24</sup> These dollar values are based on the 2005 conversion rate of 1USD= 40.25 soms

<sup>25</sup> Library of Congress 2007

village. For the 6 large villages there were 183 VHC members with approximately 24 action groups: 4-5 members per action group and 5 action groups per village.

**Training 1- Senior MOH staff in Bishkek**

Initially, the two members of the health promotion unit (HPU) situated in the family medical center (FMC) in At-Bashy center were trained at the KSHRSP office in Bishkek. One physician and one nurse were trained for 2 days, at 8 hours per day. One of the physicians was the health promotion specialist (HPS). The HPS is a full-time salaried person, based in the family medicine center in At-Bashy, who is in charge of health promotion for At-Bashy region. Since the arrival of Sprinkles in October 2005 she was involved in the Sprinkles project. She reported her monthly salary to be 1600 soms (\$39.75). From October-December 2005 her estimated time contribution to Sprinkles alone was 80%. Thereafter her time was estimated to be 50% from Jan to April 2006. The total cost of her time contribution to the intervention, based on her salary was \$95.40 (for 3 months at 80%) + \$79.50 (for 4 months at 50%) = \$174.90. For her participation in all KSHRSP activities, the HPS was remunerated 300 soms per month = \$7.45 by KSHRSP. From October 2005 to April 2006 she would receive \$52.15. Her total contribution to the distribution of Sprinkles to children during the time of the intervention was valued at \$227.05 x 62% = \$140.77.

This training was conducted by the coordinator of quality improvement. The health professionals were paid a per diem of 700 soms = \$17.39. The total for 2 days for two health professionals was \$69.56. Calculating the time the meeting cost based on wages only involved the nurse since the time for the health promotion specialist was already valued above. The time for one nurse was 16 x \$ 0.23 hour x 1 nurse = \$3.70. Total cost of the training was \$73.26 x 62% = \$45.42.

### **Training 2- Heads of FAPs/FGPs At-Bashy**

Beginning in October 2005 trainings were imbedded into monthly meetings. The second training occurred at the family medicine center (FMC) in At-Bashy with all the FAPs and FGPs during a monthly. This meeting included: the HPS and the hospital administrators (director, the deputy director and laboratory technician) as well as the FAPs and FGPs. In 2005 there were 17 villages reported involved with KSHRSP. There were six FGPs and 11 FAPs with a total of 9 physicians and 62 nurses/ hygienists/feldshers. For the second training only one member was present from either a FAP/FGP. The total number present was estimated at 21 people in addition to the coordinator of quality improvement and a trainer from KSHRP. The assumption was made that the FGP representative would be a physician and a FGP representative a nurse. An hourly wage was calculated for the nurses and doctors. Based on \$37.00/ month and 40 hours of work per week nurses have an hourly wage of \$0.23. Based on the similar calculations using \$60.00 per month salary doctors have an hourly wage of \$0.38/ hr. Costs for this training 6 doctors and 11 nurses for 4 hours was \$19.12. For the 4 senior members present (the time contribution for the HPS was calculated above) the total is \$6.08. Lunch was also provided at average of 85 soms per person (\$2.11) totaling \$ 50.64 (including the driver and the coordinator of quality improvement and the trainer). Total cost of the training was  $\$75.84 \times 62\% = 47.02$ .

### **Training 3-Training of VHC members in At-Bashy**

The VHCs were trained by the HPS and a KSHRSP trainer in the FMC. This was an informational training about the Sprinkles intervention. This training was completed in 8 hours over with lunch provided. Only the heads of each VHC members responsible for the committee on anemia were present at this meeting which

totaled 19 members<sup>26</sup>. Total value of time for the VHC during this meeting was \$44.08. Lunch was \$44.31 for 19 VHCs, the SPH the trainer, the coordinator of quality improvement and the driver. Total cost was  $\$88.39 \times 62\% = \$54.80$ .

#### **Training 4- Training/distribution meeting in FAP/FGPs**

The fourth training, conducted by the coordinator of quality improvement, the KSHRSP trainer and the HPS, was combined with the delivery of Sprinkles to the 17 FGP/FAPs before the distribution to the target group. Training participants were the FGP/FAPs, the heads of VHCs; and members of the school board. The purpose of the training was to inform all members of the FAP/FGPs about Sprinkles distribution and monitoring and inform members of the school board so that they could inform children at school and their mothers. These school board members are also volunteers and their time will be valued using the Kyrgyzstan daily wage of \$2.30. An average of 2.5 hours was spent in each village. For the doctors time was valued at  $2.5 \text{ hours} \times 9 \times \$0.38 \text{ per hour} = \$8.85$ ; for nurses<sup>27</sup>  $= 2.5 \text{ hours} \times 62 \times \$0.23 = \$35.65$ . Assuming that all VHC anemia action group members were present from the 17 villages this would be equal to 11 VHCs from smaller villages and 30 from the larger villages totaling 41 VHC members. The total value of the time of the VHC members for this training their time would be  $41 \times 2.5 \text{ hours} \times \$0.29 = \$29.72$ . For each member of the school board there were approximately 10 per village present at these trainings the value of their time was  $10 \times 17 \times 2.5 \text{ hours} \times \$0.29 = \$123.25$ . This assumes that the hourly wage for VHCs and school board members is \$0.29 and that there was 100% attendance at each FGP/FAP. The total value for the participants time for the training was  $\$197.47 \times 62\% = \$122.43$ .

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<sup>26</sup> Although there were 17 anemia groups there were 19 VHC anemia action group heads reported.

<sup>27</sup> The assumption here, based on interview reports, is that all of the 62 employees are nurses although some maybe feldshers or hygienist.

**KSHRSP trainers' time and per diem**

The KHSRP trainer was a facilitator for 3 trainings for over 4.5 days. The monthly salary for the trainer was \$250 and for the daily salary this was \$8.06. The financial value for the times the trainer spent conducting trainings in At-Bashy was  $\$36.27 \times 62\% = \$22.49$ . This trainer was based in At-Bashy and therefore did not receive per diem during these trainings.

KSHRSP employees who travel to sites outside of Bishkek are awarded a per diem of 70 soms per day = \$1.74. The coordinator of quality improvement estimated once per month visits to different Sprinkles sites. Each visit would be 3 days. For these visits from September 2005 to April 2006 the total per diem for the coordinator of quality improvement was  $\$41.76 \times 62\% = 25.89$ .

***Impact evaluation costs***

Five Kyrgyz physicians from the Department of Pediatrics from the regional hospital in Bishkek conducted in program evaluation activities. These physicians were involved in the testing of and registration of Sprinkles in Kyrgyzstan as well as conducting all surveys (baseline, 3month monitoring visit and 6 month follow-up). The research team (research team) was awarded a daily allowance as well as transportation fares to and from Bishkek (their home cities) and travel between villages in At-Bashy. The research team was paid a daily per diem as well as being reimbursed for travel to and from Naryn between villages located in At-Bashy. At baseline six research team members spent a total of 17 days in the intervention sites in At-Bashy raion and 18 days in the control sites in Kochkor and Naryn raion. The total amount they were reimbursed by KSHRSP was \$1680.59. Three months later they spent 10 days in At-Bashy. Reimbursement was \$1217.48 At the 6 month follow-up, 5 of the research team spent 15 days in the intervention sites and 19 in the control sites

and were reimbursed \$1410.89. The total reimbursement for the involvement of the research team in all the surveys was  $\$6217.38 \times 62\% = \$3854.78$ .

### **Participants' time for survey participation**

Mothers of the 444 eligible children and eligible pregnant and lactating women were surveyed by the doctors in the intervention site at baseline. The time spent in the intervention site for all three surveys was 42 days by the RT. The assumption is that this is also the time the participants spent being surveyed. The daily wage used to value the participants' time was \$2.32, Kyrgyzstan's 2005-2006 daily wage. Consequently, the value of the time participants spent being surveyed could be valued at  $42 \text{ days} \times 2.32 = \$97.44$ . Only 62% of their time was attributed to the children in the survey. Therefore the total value of the participant's survey time for the 444 children was \$60.41.

### ***Sprinkles Distribution***

Sprinkles were delivered to 4300 eligible 6 to 36 months old in At-Bashy. Although the responsibility for distribution was placed on the FAPs/FGPs reports varied regarding the degree to which both FAP/FGP and VHC members participated in the distribution. In smaller villages, FAPs had fewer staff members, and VHC anemia action group members assisted with the distribution.

The end goal for this analysis was to estimate the time contribution of all those who participated in the Sprinkles distribution. Ideally, this required knowing the number of households involved in the 17 villages involved in the intervention<sup>28</sup>, the number of children 6 to 36 months old per household, the time to complete distribution to all households with eligible children (this included the time spent per household and

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<sup>28</sup> Although there are 19 villages in At-Bashy, At-Bashy center and Ashkar are not included since they were reported to have no VHCs and At-Bashy was the raion center.

the travel between households) and as well as the FGP/FAP and VHC members involved in distribution. Not all information was available at the time of cost data collection. Data on the number of household per village , the FGP/FAP and VHC members involved in distribution and the time spent distributing Sprinkles were collected from interviews of a sample of VHCs and FGP/FAPs from different villages. These data were used to impute values for those villages for which those data were not collected. Table 2 shows the number of households for each village as well as the number of doctors, nurses who staff the FGP/FAPs in each village during the time of the intervention on 2005 and the estimated number of VHC members per village. The assumption was made that there was one child age 6 to 36 per household.

Estimates were that one person would require 7 hours to cover 10-20 households. The number 10 was used since it allowed for 5 hours of time visiting households (20 minutes per household) and 2 hours travel time between households. The total cost for the time for distribution was computed as follows: for each village the number of households containing children (assuming 1 child per household) was divided by the number of staff per FAP/FGP<sup>29</sup> and VHC members involved. This identified the number of households that each staff would have been responsible for given that the number of households were evenly allocated across staff members. The number households each staff was responsible for was divided by 10 (the number of households that was reported to be completed in 7 hours during interviews). This number was then multiplied by 7 to obtain the number of hours expended to distribute Sprinkles in each household. This resulted in the number of hours each person contributed to distribution. This final number was then multiplied by the hourly salary of each participant. The total value for distribution of Sprinkles to 4300 children between 6 and 36 months was \$233.36. The value of the mothers' time during

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<sup>29</sup> The assumption here was that all staff participated in each FAP/FGP

distribution was calculated as 4300 mothers x 20 minutes per mother ( the time spent per household during distribution as estimated by mothers and staff interviewed) /60 minutes x \$0. 29 = \$415.67.

### ***Monitoring***

After distribution the VHC and FAP/FGP members visited households to monitor how Sprinkles were being taken and to motivate mothers to continue giving their children a weekly dosage of Sprinkles. This monitoring time also involved discussions and counseling about side effects. Side effects reported included constipation, nausea and diarrhea, however no treatment was provided and participants were encouraged to continue taking Sprinkles. VHC and FGP/FAP members interviewed were asked to estimate the frequency with which they visited households. On average, households were monitored 1.2 days per week<sup>30</sup>. We estimated that each person would dedicate 8.4 hours per week and a total of 168 hours for the 5 months during the intervention monitoring homes<sup>31</sup>. Only nurses and the anemia action group VHC members were included in the calculations of the monitoring visits. Nurses often visited with mothers as part of their duties and the assumption was made that the FGP/FAPs involved in the distribution were not physicians since they were often assigned administrative duties. The value of time spent monitoring households by 62 nurses<sup>32</sup> and 41 VHC members for the 5 months of the intervention was \$4393.20. This monitoring was for all participants. For children alone the value of the time spent monitoring was equivalent to \$4393.20 x 62% = \$2723.78.

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<sup>30</sup> VHCs and FAP/FGP members also reported that they spoke to mothers outside of households informally, in passing, these instances were not included in the estimate.

<sup>31</sup> This included time for travel between households

<sup>32</sup> The assumption here was that all the nurses in the FAP/FGPs were involved in the monitoring of Sprinkles consumption.



To estimate the mother's time spent during monitoring this would be equivalent to the number of hours spent by both the nurses and the VHCs not including travel time. Based on the above calculations, nurses and the VHCs each completed 18 households per week. This would mean 6 hours of visiting with mothers per week. For the entire 5 months the value of the time the mothers spent would be equivalent to  $120 \text{ hours} \times 103 \text{ (VHCs + nurses) mothers} \times \$0.29 = \$3584.40 \times 62\% = \$2222.33$ .

One month after distribution, the At-Bashy health promotion specialist and the health promotion unit nurse visited each village to monitor the progress of Sprinkles. They reported spending 3 hours per village discussing Sprinkles with those involved in the monitoring. The health promotion specialist reported that this was conducted in 6 days (8 hours per day with travel included). The time for the health promotion specialist was valued above but the value of the time of the nurse assisting her would have been  $6 \times 8 \text{ hours per day} \times \$0.23 = \$11.04 \times 62\% = \$6.84$ . The total value of time for those involved in Sprinkles in each village was calculated to be 62 nurses and 41 VHCs. The value of their time for this meeting was  $62 \times \$0.23 \times 3 \text{ hours} = \$42.78$ . For VHCs the value was  $41 \times \$0.29 \times 3 = \$35.67$ . The total was  $(\$42.78 + \$35.67) \times 62\% = \$48.64$ .

### **Monitoring Meetings**

During the 6 months of the intervention, health promotion unit and FGP/FAP staff and VHCs participated in different meetings where Sprinkles activities were discussed. The VHCs held their own bi-monthly meetings and the heads of the VHCs also participated in monthly meetings with the health care professionals at the family medical center (FMC), where the health promotion unit was housed, in the rayon center At-Bashy. The health professionals also attended monthly meetings at the FMC but only discussed Sprinkles on a quarterly basis.

The bi-monthly VHC meetings were held for 2 hours and the average reported time spent discussing Sprinkles during the 6 month intervention period from November to April was 30 minutes per session. Assuming fixed and 100% attendance, the time spent discussing Sprinkles was constant across the months of the intervention, the value of the time spent in VHC meetings discussing Sprinkles was calculated as follows:  $238 \text{ VHCs} \times 6 \text{ hours for 6 months} \times \$0.29 = \$414.12$ . The value of estimated time spent in discussions regarding Sprinkles for children =  $\$414.12 \times 62\% = \$256.75$ .

Meetings at the FMC in At-Bashy occurred monthly, Sprinkles was discussed every quarter. The assumption made was that a meeting occurred in February, June and October of every year in which Sprinkles were discussed. In the 6 month period during the intervention these meetings would have only occurred once (not including that one meeting would have been used for the training that occurred in October 2005, which was valued above). Assuming full attendance at these meetings of all health staff (9 doctors, 62 nurses, the health promotion specialist and 2 chief physicians), the value of time spent discussing Sprinkles is as follows: The meetings lasted 3 hours and Sprinkles was discussed for, on average, 60 minutes. Value of the time of the doctors was  $11 \text{ doctors (the time of the HPS was already valued above)} \times 1 \text{ meetings} \times 1 \text{ hour time focused on Sprinkles} \times \$0.38 \text{ hourly salary for doctors} = \$4.11$ . For nurses  $62 \text{ nurses} \times 1 \text{ meetings} \times 1 \text{ hour time focused on Sprinkles} \times \$0.23 / \text{hour} = \$14.26$ . The total for the meetings were  $\$18.44 \times 62\% = \$11.43$ .

Every month, MOH health staff in At-Bashy raion as well as VHCs traveled to the FMC to meet and discuss health activities being carried out in the communities. On average it was estimated that 60% of the doctors and 80% of nurses were in attendance with the 19 VHC heads. Total number of participants plus the HPS was 75. These meetings were on average 2.5 hours. During the Sprinkles intervention the average time spent discussing Sprinkles was 60 minutes. The value of this meeting was

calculated as: for VHCs 6 hours (for 6 months) x 19 x \$0.29 per hour=\$32.77. For doctors, 6 hours (for 6 months) x 5 x \$0.385 per hour = \$11.40. For nurses 6 hours for (6 months) x 50 x \$0.23 per hour = \$69.00. Total value for this meeting was \$113.17 x 62% = \$70.16.

#### Travel time and expense

Travel between At-Bashy and the different villages for meetings were paid for by the MOH staff members and VHCs involved. To calculate travel time and expense, all villages in the At-Bashy raion were plotted using digital mapping software (Geographic Information system) and brought into Google earth. Distances between all villages and At-Bashy center were measured (using the visible main routes). Each person interviewed was asked to estimate the average time spent traveling one way to monthly meetings as well as the cost for travel. Thirteen of the 18 interviewed reported times and costs spent traveling from 5 villages to At-Bashy center. These responses were related to the other 12 villages using the digital maps. For example, a nurse living in Ak-Muz reported that it took her 1 hour to travel to the monthly meetings. Ak-Muz was measured to be roughly 29km away and it cost her 30soms (\$0.75). On the digital maps Ak-Moyun, and Taldysoo were in close proximity to Ak-Muz and were measured to be 20 and 35 km from At-Bashy respectively. Using the distances and times for Ak-Muz those for Ak-Moyun and Taldysoo were calculated at 38 and 65 minutes of travel respectively. Estimates of travel time were derived for each village accordingly. The travel costs reported regardless of the distance was 30soms (\$0.74 one way and 60 soms return (\$1.49).

The health promotion specialist and nurse travelled in a taxi to all 17 villages over a period of 6 days. The cost of travelling to 17 villages would be equivalent to \$29.84 round trip. The value of the travel time was a total of 1460 minutes (roundtrip).

Assuming that they divided the time and the trips equally, the value of the time the HPS spent traveling was  $12.17 \text{ hours} \times \$0.38 = \$4.62$  and for the nurse the time value was  $12.17 \text{ hours} \times \$0.23 = \$2.80$ . The total economic cost of travel was  $\$37.26 \times 62\% = \$23.10$ .

For the 1 quarterly meeting the cost of travel for 9 doctors, roundtrip, from each of their villages to At-Bashy was \$17.16. The value of the travel time for the doctors was  $14.1 \text{ hours} \times \$0.35 / \text{hour salary each} = \$4.93$ . Travel time for nurses was 88.43 hours total and was valued as  $88.43 \text{ hours of travel} \times \$0.23 \text{ per hour} = \$20.34$  with a round trip cost of \$104.23. The total cost for travel for quarterly meetings was  $\$146.66 \times 62\% = \$90.93$ .

Each month the travel cost for doctors would be  $60\% \times (\$17.16 + \$4.93) = \$13.25$ . For the nurses the cost would be  $80\% \times (\$20.34 + \$104.23) = \$99.66$ . For VHCs the cost was  $27.7 \text{ hours of travel roundtrip} \times \$0.29 \text{ per hour} = \$8.03$ . The VHCs paid \$34.08 for the total round trip visits to meetings in At-Bashy. Total cost for monthly meeting travel was  $\$155.02 \times 62\% = \$96.11$ . For 6 months of the intervention the total cost of travel was \$576.67.

### ***Transportation and Lodging***

Although KSHRSP had a fleet of cars and drivers, they also rented drivers with their own cars, during the period of the baseline survey and monitoring. Further, travel accommodations were provided for staff and consultants working for the KSHRSP. Over the period of the survey, transportation was used for travel to intervention and control raions as well as transportation between villages. These cars were used by KSHRSP staff. For the majority the coordinator of quality improvement used these cars for monitoring trips. The total expense for these trips was  $\$2528.67 \times 62\% = \$1567.78$ . For accommodations, we used the 24 month income statements of

KSHRSP and calculated the monthly expenses for accommodations and multiplied this by 6 for the number of months the intervention lasted. The total cost of accommodations was  $\$691.33 \times 62\% = \$428.62$ .

### ***4.2.3. Data Analysis***

#### *4.2.3.1 Cost-effectiveness analysis*

This analysis was intended to assess the cost per child per 1 g/L change in hemoglobin concentration with weekly doses of Sprinkles. In this incremental analysis, the comparator was the strategy that is the current practice in the intervention area for IDA prevention (no current intervention). That is the counterfactual used was “do-nothing”.

#### *4.2.3.2 Sensitivity Analysis*

Assumptions made throughout the analysis regarding costs not directly measured that could have significantly changed the final cost-effectiveness ratio (CER) were subjected to sensitivity analyses. We present results for individual assumptions that had a dollar impact on the final CER, as well as the combined effect of these assumptions on the final costs per g/L change in hemoglobin concentration.

#### *4.2.3.3. Digital Mapping and Elevation*

To calculate distances between villages, the latitude and longitude coordinates (in decimal degrees) of all communities in At-Bashy were found using Fuzzy Gazetteer. The FuzzyG results were converted into a KML file that graphically displayed the results in Google Earth. A program was written with a script to run a FuzzyG query against each of the community names, and compile the top 10 results from each query into a table, which contains a total of about 300 place names. A

digital ruler was used to measure the distances between each community and the center of At-Bashy in kilometers.

Final costs were calculated using Microsoft Excel 2007. Effectiveness data were analyzed using SPSS 15.0. Significance of the change within groups in the prevalence of anemia between pre-and post-intervention was tested using McNemar's test and a Z-test using the chi-square statistics from the McNemar's test to evaluate whether differences between treatment groups were different between pre-and post-intervention.

### **4.3 RESULTS**

#### ***4.3.1 Financial and Economic Costs of the Sprinkles Programme***

The total estimated economic cost of the KHSRSP weekly supplementation Sprinkles intervention for children 6 to 36 months for 6 months, including preparation and planning work carried out by KSHRSP staff was \$35,068.55<sup>33</sup> and the cost per child was \$8.16. Financial costs were 53% of the total costs with the cost of Sprinkles being 81% of the financial cost. The highest opportunity costs (which included the costs for paid and unpaid labor) were related to the value of the time contributed to planning and monitoring (this included the household visits for the monitoring of compliance of the Sprinkles intervention by the VHCs and the FGP/FAPs). The major opportunity cost was the value of the time of those involved in monitoring. The KSHRSP staff time accounted for 48% of opportunity costs. This time included the planning and preparation for the Sprinkles impact evaluation and intervention program (times spent on these two activities could not be separated).

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<sup>33</sup> The evaluation component of the intervention was not included in the final costs since the program could have been conducted without these activities.

#### ***4.3.2 Evaluation of impact of Sprinkles on mean hemoglobin levels and anemia prevalence***

A total of 743 children were included in the study at baseline (pre-intervention), 434 in the group that received Sprinkles and 309 in the group that did not (Table 4.2). The two groups did not differ by age, hemoglobin concentration, family size nor the frequency with which their mothers consumed meat ( $p>0.05$ ). The intervention group communities of children did reside at a mean higher altitude, which was highly statistically significant ( $p<0.001$ ) however, the mean difference was only 153 meters, which was unlikely to be biologically significant. The intervention group had a higher percentage of boys, children whose families owned 1-20 sheep or goat, who leased their own land and who owned more cows or horses. Further, a smaller percentage of the children in the intervention group had mothers who had been to technical college or university ( $p<0.05$ ). The majority of these differences may be explained by place of residence, because 19.4% of the children in the intervention group resided in urban areas compared to 37.0% in the control groups (Table 4.2).

##### ***4.3.2.1 Receipt of Sprinkles and Compliance***

All of the children selected for the evaluation received Sprinkles, resulting in 100% coverage. Compliance was defined based on the number of empty sachets found at a follow-up visit 3 months after the intervention started. We estimated that the children consumed 92.5% of the Sprinkles they received (a mean of 22.2 sachets and SD of 8.3). Only 1.6% of the mothers reported sharing Sprinkles and over 91% reported that the child ate the whole portion of food mixed with Sprinkles.

#### *4.3.2.2 Unadjusted Mean Hemoglobin and Anemia Prevalence*

Based on unadjusted anemia prevalence, in the group that received Sprinkles there was a significant decrease in anemia prevalence from 63.4% to 55.6% at 6 months follow-up ( $p<0.001$ ; McNemar's test) (Table 4.3). Table 4.2,  $p=0.18$ ). Anemia prevalence in the control group (children not receiving Sprinkles) was not significantly different ( $p=0.22$ ) between the pre-intervention (69.6%) and post-intervention (67.7%) periods.

Furthermore, mean hemoglobin levels were 4.1 g/L higher in the Sprinkles group at 6 months post-intervention compared to baseline ( $p<0.05$ ), and 4.8 g/L higher than in the control group post-intervention ( $p=0.001$ ). In the control group the difference in mean hemoglobin levels between baseline and 6 months follow-up was 1.1 g/L ( $p>0.05$ ). Pre-intervention mean hemoglobin levels were not significantly different between the 2 groups. When adjusted for age and sex, patterns did not change significantly (Table 4.3).

#### *Sub-group Analysis*

The assumption that the impact of the Sprinkles was similar across all age groups was examined using sub-group analyses. Age distributions comparing mean hemoglobin at 6 months for Sprinkles and control groups indicated a trend towards higher differentials in mean hemoglobin levels, between the Sprinkles and control groups, among older (24-36 months) than younger children (Figure 4.1). Differences observed between 15-23.9 month olds were marginally significant ( $p<0.06$ ). Changes in anemia prevalence from pre- to post-intervention were also largest for the Sprinkles group between the ages of 24 to 36 months (Figure 4.2). This pattern was confirmed when the difference between these differences were calculated (Figure 4.3). Sub-group multivariate regression analyses were conducted based on these trends in the data (Table 3.3).



**Table 4.2** Baseline characteristics children 6-to-36 month old in Sprinkles and control group

	Sprinkles Group n=434	Control Group n=309	P Value**
Age (months)	20.6 (8.6)	19.59(8.4)	0.125
Altitude ( meters)	2193.6 (131.5)	2039.7 (317.9)	0.0009
Hemoglobin (g/L)*	100.6 (18.4)	98.8 (18.0)	0.180
Family Size	5.6 (1.5)	5.7 (1.8)	0.778
<b>Place of Residence</b>			
Urban	19.4	37.0	0.0006
<b>Sex (%)</b>			0.017
Male	60.6	51.8	
Female	39.4	48.2	
<b>Education Level (%)</b>			0.041
Basic Education	65.0	57.2	
Higher Education	35.0	42.8	
<b>Ownership of Sheep/ goat (%)</b>			0.0003
None	28.5	39.5	
1-20	71.5	60.5	
<b>Cows/Horses (%)</b>			0.0003
None	26.2	38.6	
1-20	73.8	61.4	
<b>Ownership of Land (%)</b>			0.0003
Not using own Land	22.4	43.5	
Leasing Own Land	77.6	56.5	
<b>Mother's Meat Consumption in past 3 days (%)</b>			0.753
None	23.5	23.5	
1-3 times	76.4	76.4	

\*Hemoglobin was adjusted for altitude using Asian-specific correction factors (see Chapter 1).

\*\* P-values represent the comparative difference between the Sprinkles and Control groups at baseline

Values are either percentages or means (standard deviations).

**Table 4.3** Mean hemoglobin concentration and anemia prevalence for intervention and control groups pre- and post- intervention

	Intervention Group (received Sprinkles)	Control Group (did not receive Sprinkles)
<b>Anemia Prevalence</b>		
(Hemoglobin < 110 g/L, % unadjusted)		
Anemic pre-intervention	63.4	69.6
Anemic post-intervention	55.6	67.7*
Mean Hemoglobin (g/L)		
Pre-Intervention (unadjusted)	100.6 (0.9) N=434	98.8 (1.0) N=309
Post-Intervention( unadjusted)	104.7 (0.9)** N=342	99.9 (1.2)* (p=0.001) N=260
<b>Anemia Prevalence</b>		
(Hemoglobin < 110 g/L, % adjusted for age and sex)		
Anemic pre-intervention	63.4	69.3
Anemic post-intervention	55.8	70.2*
Mean Hemoglobin (g/L)		
Pre-Intervention (adjusted for age and sex)	100.1 (0.1) N=434	98.1(0.1) N=309
Post-Intervention( adjusted for age and sex)	104.4 (0.1)** N=342	99.2 (0.1)* (p=0.001) N=260

Values are percent or means (standard error). \*Different from Sprinkles group, P<0.05; \*\* different between baseline and follow-up (within group).

#### 4.3.2.3 Difference in Difference Impact analysis

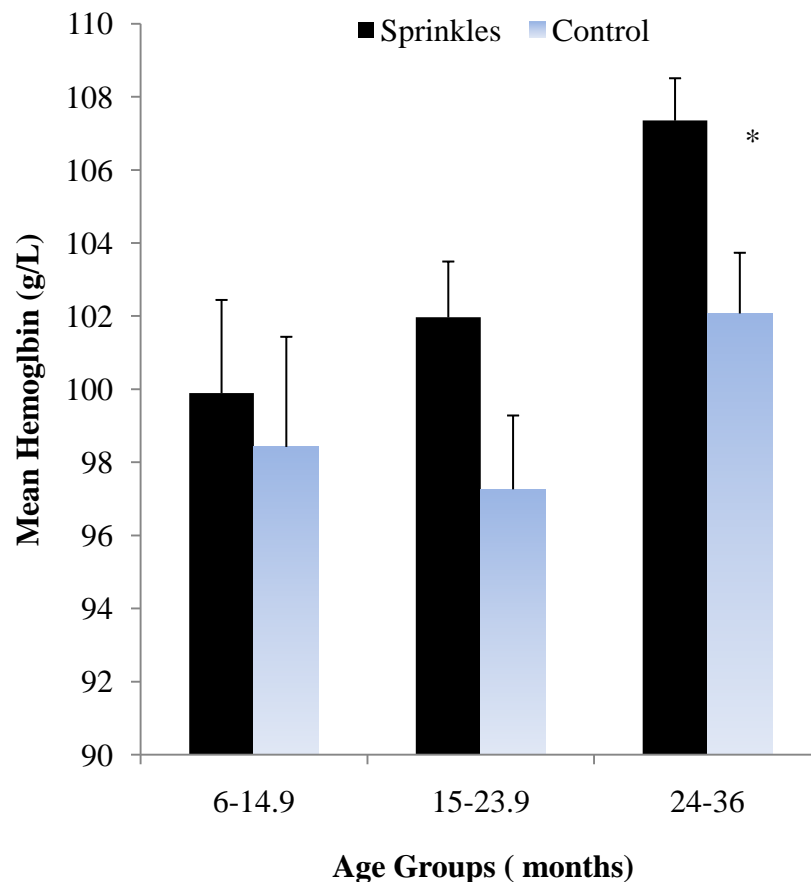
Using a multivariate regression framework, impact was assessed based on the difference between pre- and post-intervention mean hemoglobin concentration of the intervention group relative to the control group. This multivariate regression analyses was adjusted for individual level variables that had a significant relationship with hemoglobin concentration such as; age, sex, baseline anemia status, family ownership of sheep or goat, family use of own land, residence in an urban or rural area, mother's

consumption of meat in the three days prior to the survey and pre-intervention anemia status (Table 4.3, column A). Only estimates for those variables that varied significantly with the hemoglobin levels are presented in Table 4.3, column A. After adjustment, the difference in average hemoglobin in the Sprinkles group before and after treatment was 6.0 g/L higher than the difference in the group that did not receive Sprinkles (control) before and after the intervention period.

The relationships between covariates and hemoglobin in this multivariate model were similar to those reported in Chapter 3 for all children at baseline (see Table 3.3).  $p < 0.001$  Hemoglobin decreased significantly ( $p = 0.008$ ) by 0.7 g/L for every month increase in age of the children, however, this relationship decreased by 0.02g/L with increasing age ( $p = 0.001$ ). Boys had a significantly lower hemoglobin level than girls (2.3 g/L,  $p = 0.005$ ). Among families who did not use their own land, mean hemoglobin was 13.3 g/L for those families who owned 1-5 sheep or cattle than for those who owned 20 or more sheep ( $p = 0.026$ ).

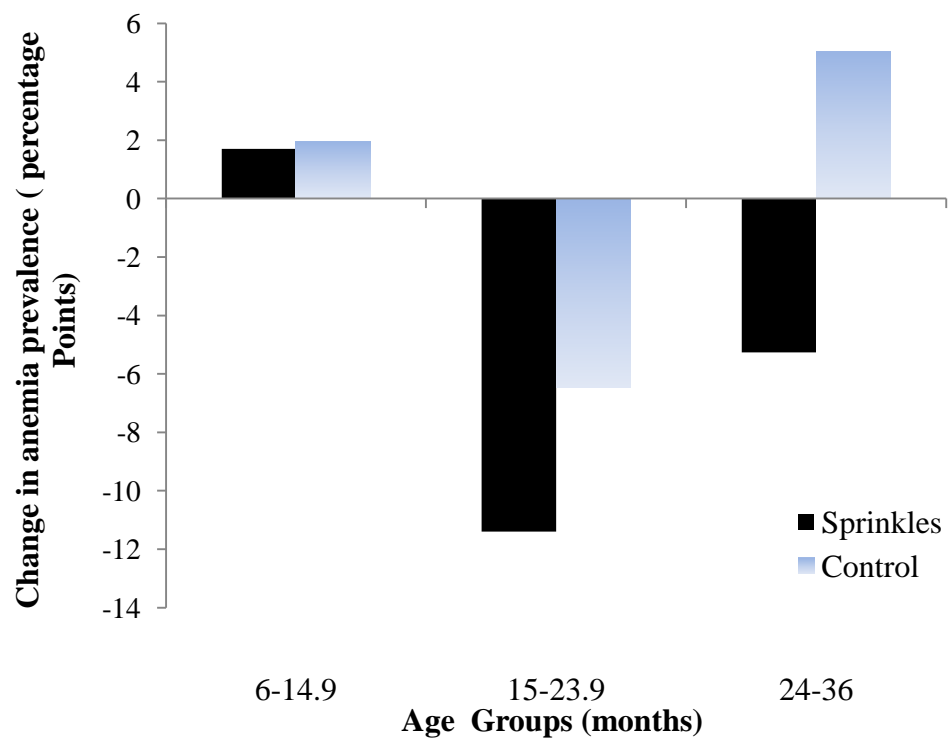
#### Sub-group Impact analysis

Based on the significant results of our bi-variate analyses, we conducted sub-group regression analysis to determine whether the impact of Sprinkles differed based on age. Impact was assessed for children age 24-36. Within this group, the difference in difference of average hemoglobin between the control and treatment groups pre- and post- intervention was 8.2 g/L ( $p < 0.001$ ) Table 4.4 Colum B).

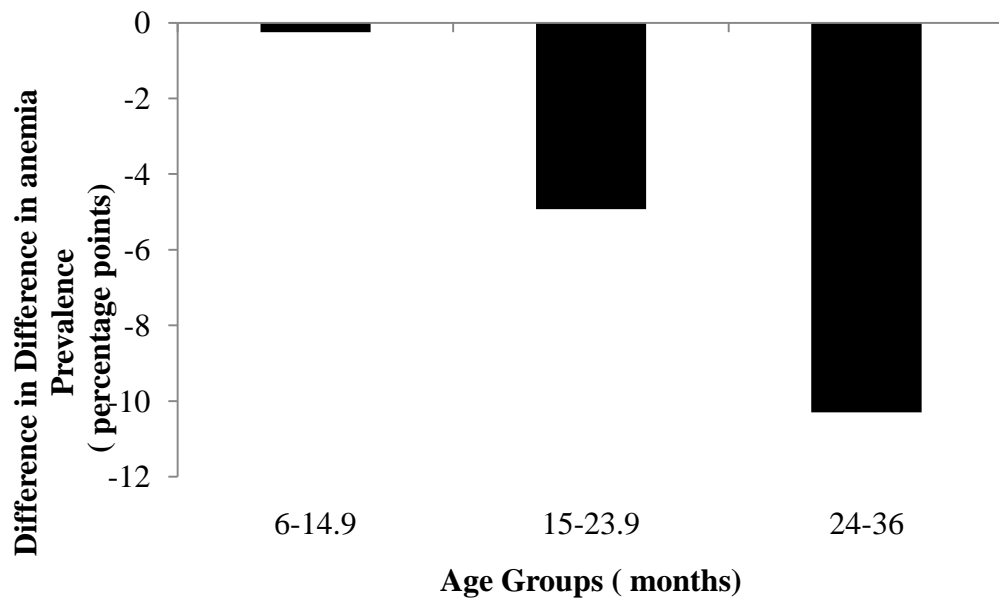


**Figure 4.1:** Mean hemoglobin for Sprinkles and control group at post-intervention (6 months follow-up). Values are unadjusted mean and standard errors (SE).

\* Control group were significantly different from the Sprinkles group,  $p < 0.05$  among 24-36 month old. Among 15-23.9 month olds significance was marginal ( $p < 0.06$ ).



**Figure 4.2:** Changes in anemia prevalence from pre-to post-intervention between the control and Sprinkles intervention groups by age. \*Significantly different from Sprinkles ( $p < 0.001$ ).



**Figure 4.3:** The change in anemia prevalence from pre-to post-intervention were calculated for both the control and intervention groups and then the differences between these two groups were then calculated. Negative percentage points indicate that there was a greater decrease or less of an increase in anemia prevalence for the Sprinkles than the control group. Positive quantities indicate where the anemia prevalence either decreased or had a smaller increase than the control group.

**Table 4.4:** Sub-group Impact Analysis

Variables	Column A 6 to 36 months old	Column B 24-36 months old
Intercept	86.5 (3.8)**	84.3** (11.2)**
Time (ref=post) <sup>2</sup>	12.1 (1.4)**	19.3(2.3)* *
Treatment <sup>3</sup> ( ref=control)	6.8(1.4)**	1.2(2.0)
<b>Time*Treatment difference<sup>4</sup></b> (ref=control post-intervention)	<b>6.0(1.7)**</b>	<b>8.2(2.7)**</b>
Age	-0.7(0.3)**	
Age*Age	0.02 (0.01)**	
Sex (ref=female)	-2.3 (0.8)**	
Urban residence (ref=rural)	5.4(3.0)**	
Baseline anemia ( ref= anemic)	26.3(1.2)**	28.2(1.8)* *
Ownership of Sheep/Cattle and Land		
None x Not using own Land	-7.0 (5.6)	
1-5 x Not using own Land	-13.3(6.0)*	
6-20 x Not using own Land	-6.4(5.7)	
>20 x Not using own Land	Ref	

Ref = reference group.

<sup>1</sup>A random effects regression analysis was used. Values are regression coefficient (standard error). The dependant outcome is hemoglobin values in g/L.

<sup>2</sup>This coefficient represents the difference between pre-and post-intervention which captures the aggregate factors that would cause changes in hemoglobin in the absence of an intervention

3. This coefficient represents the difference between the Sprinkles and control group post-intervention.

4. This coefficient is an interaction term which represents the difference in the differences between the mean hemoglobin of the Sprinkles and intervention group between pre-and post-intervention.

\*P<0.05, \*\*p<0.01



#### ***4.3.3. Cost-effectiveness***

The results of our cost-effectiveness analysis integrate results from our cost analysis and our impact analysis. The final cost effectiveness ratio calculated was the cost per child per g/L change in hemoglobin. The cost for the intervention calculated above was \$35,068.55 and 4300 children were treated with Sprinkles. The cost per child was \$8.16 and the cost per child per g/L change was \$1.36. This varied according to the components of the program activities included. If this intervention were to be repeated in the same or another raion the cost would decrease to \$22,960.94 and the cost per child would \$5.33 and the cost per child per g/L \$0.89 since planning and other initiation activities would not have to be included. Further, the majority of the KSHRSP time would be eliminated since the raion trainers, the MOH staff and the VHCs would be able to distribute and monitor Sprinkles on their own. Using the impact results from the sub-group analysis for the oldest children (24 to 36 months) our cost-effectiveness ratio would become as low as \$0.99 per child per g/L.

#### ***4.3.4. Sensitivity Analysis***

First, our assumption that 62% of the costs of the intervention activities could be attributed to distribution to children alone was based on the ratio of the number of children to the number of women who received Sprinkles assuming that each household that had children had no other recipients of Sprinkles. If all efforts were attributed to distributing Sprinkles to the children then the CER would increase to \$2.19 per g/L per child. At the most conservative end of the assumption, if each household containing 1 child 6 to 36 months also contained a pregnant or a lactating

mother then efforts for children alone would only be in 20% of the households<sup>34</sup>. The CER would become \$0.55.

Staff time was estimated based on the assumption of 100% attendance. Monitoring was assumed to be done by all the nurses and all the VHCs involved in the anemia action groups. If only 50% of these were involved in monitoring then the cost per child would decrease by \$1.06 but the cost per child per g/L only decrease to \$1.18<sup>35</sup>. Finally, although the price of Sprinkles was fixed we assessed the effect of varying the price of Sprinkles since that was the largest financial cost. The cost of Sprinkles used for daily supplementation has been reported elsewhere as \$0.01 per child<sup>33, 34</sup>. If the cost of Sprinkles in this study were reduced from \$0.10 per child to \$0.01, the CER would become \$0.95 per child per g/L. With the combined effect of these individual analyses the CER would decrease to \$0.40 per child per g/L.

#### **4.4 DISCUSSION**

Based on our analysis, the cost-effectiveness of 6 months of weekly home-based fortification with Sprinkles for the treatment and prevention of anemia in 6 to 36 month old children in At-Bashy region of Kyrgyzstan was \$1.36, with a range of \$0.40 to \$2.19 based on sensitivity analysis (this range would become \$0.27 to \$1.49 if the focus were only children 22 to 36 months). Without KSHRSP as a delivery system the estimates decrease to a mean of \$0.63 per child per gram of Hb (with a range of \$0.28- \$0.98 based on sensitivity analysis). This estimate would also be similar if this intervention were repeated in another village within the Naryn oblast.

The highest financial cost was the cost of Sprinkles. If Sprinkles were available locally at the cost of \$0.01 per child the CER would range between \$0.40 and \$0.98.

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<sup>34</sup> Households where mothers were not taking Sprinkles which would be 1700 households with 2 children per household.

<sup>35</sup> Decreasing the staff involvement and increasing the number of children per household for distribution did not have any overall effect on the CER.

Forty-four percent of opportunity cost was due to the MOH staff and the VHC members' time contributions and 56% of the opportunity cost was due to the KSHRSP staff contributions (this included the time and value of the Sprinkles registration). The majority of the KSHRSP staff costs were for per diem. The monitoring of Sprinkles done by the VHCs and the FGP/FAP staff contributed to 75% of the value of their contribution. With distribution alone and no monitoring of intake, the cost per child per g/L change in Hb would be \$0.20. However, monitoring by the VHC and MOH staff was an important activity that contributed to maintenance of compliance and contributed to the observed effectiveness<sup>29</sup>.

The cost per child was \$8.16. In 2005 9.6% of the Kyrgyz population was 0-4 years old<sup>30</sup>. Based on this percentage, assuming uniform countrywide costs, the cost of providing Sprinkles for all 499,584 children for 6 months would be approximately \$4 million.

When compared with costs of iron supplementation reported in the past, the cost of home-based fortification with Sprinkles was in the upper range of costs. Estimates of the cost per child, in 1984, of iron supplementation programs were between \$3.17 and \$5.30 (present value, using a 3% interest rate: \$4.79 to \$8.02)<sup>31</sup>. In 1985 Horton estimated the cost of micronutrient supplementation per person-year to be \$4.00; present value: \$7.89<sup>32</sup>. Levin's estimates, based on a review of studies of anti-anemia programs, were between \$4.58 and \$7.14 (present value: \$10.48 and \$16.34) per year per capita total for supplementation of population of 1000 with ferrous sulphate and ascorbate by one health staff<sup>33</sup>. For our population of 4300 children, assuming a proportional increase in cost of staff and supplements, this value would be between \$20.47 and \$70.24. Our present estimate of \$8.16 per child falls well below this range. Further, these higher estimates would result in cost-effectiveness range between \$9.78 and \$32.52 for a 6 month iron supplementation

intervention. Given these comparisons, the Sprinkles program would be more cost-effective; however, these results must be interpreted cautiously since they were based only on the number of participants served and supposition that the costs of staff and equipment were constant.

Based on our review of the literature, this is the first cost-effectiveness study specific to weekly home-based fortification with Sprinkles. Further, the only economic analysis found of iron supplements to reduce anemia was a benefit-cost analysis by Levin (1986) mentioned above. Other economic studies, assessing the cost-effectiveness of oral iron supplementation in preventing anemia, have expressed final results as cost per averted disability-adjusted life year (DALYS)<sup>26, 34</sup>. These studies have translated cases of neonate and female mortality due to severe anemia into years of disability and death. In our case, although iron-deficiency anemia in childhood can impact the growth and development of pre-school aged children<sup>4, 34</sup> translating these anemia- induced outcomes into DALYS would require a series of tenuous assumptions that would lead to questionable final estimates.

Although there are no other studies evaluating the cost-effectiveness of Sprinkles, to provide a context for our results, we compare our results to those of other closely related studies. First we look at economic studies done using Sprinkles; second we use effectiveness results from other Sprinkles distribution programs (assuming similar costs) and calculated cost-effectiveness using our cost results.

In 2006, Sharieff et al., using models, linked improvements in Hb concentrations of 6-8 month old children receiving daily iron supplementation with Sprinkles to increases in IQ points and gains in future earnings at age 18<sup>35</sup>. They found that children in the intervention group, with 12g/L mean higher Hb than those in the control group would have 2.1 points higher IQ and an average higher gain in earnings of \$2.33 annually at 18 years. Using a similar method, based on a Kyrgyz,

2005 per capita GDP of \$473 and mean difference in Hb of 6.0 g/L between intervention and control children 6-8 months in our study, we found an annual average gain of \$1.17 in earnings for weekly supplementation with Sprinkles. These results may be interpreted to support weekly supplementation with Sprinkles having an impact on the future earnings of children as well. Although our results are indicative of a positive impact of Sprinkles on future earnings, there is some uncertainty in the comparison due to the small sample sizes used to calculate the results.

The effectiveness of Sprinkles has been evaluated in the context of a World Vision large-scale integrated nutrition programs in Haiti<sup>36</sup>, and Mongolia<sup>23</sup>. In Haiti, children 9-24 months received a daily dose of Sprinkles containing 12.5 mg of iron in addition to wheat-soy blend food rations. In Mongolia, children 6-35 months received Sprinkles containing 40mg of iron. The average mean change in hemoglobin in Haiti was 10.9g/L which would result in a CER of \$0.75 (assuming our calculated costs and population served applied) which is half our estimates for weekly supplementation. These estimates may have also been lower than due to a higher impact, which may have been attributed to the fact that the children in the Haiti received an iron-fortified wheat-soy blend food. Further, children received daily supplementation. This estimate must be interpreted keeping in mind that distribution efforts and costs may have been less for the Haiti and Mongolia programs since Sprinkles were distributed in the context of integrated nutrition programs which may not have required additional monitoring as with our VHCs.

Other studies have dealt with the cost-effectiveness of anemia reduction using anti-helminthic treatments<sup>37, 38</sup>. These studies reported the cost-per case of anemia prevented to be between \$1.70 and \$9.51. If our results were converted to cost per case of anemia prevented we would arrive at estimates of \$104.55 which are much higher. This is mainly because although they had higher total costs for implementing

their programs, their delivery systems were school-based and allowed them to reach a larger number of children over a longer period of time at a lower cost.

Lechtig et al (2006) assessed the cost-effectiveness of a weekly micronutrient supplementation program. The cost per covered participant per year was \$6.04 and a cost-effectiveness ratio of \$.50 per 1% of protective effect<sup>39</sup>. Although the population included women, adolescent girls and children under 5 years, if our results were calculated similarly these estimates are lower than our estimates of \$8.16 per child treated for 6 months and CER of \$0.91 per 1% protective effect. However, details on the delivery system used in this intervention, and associated costs of training and monitoring was not available and limits a full comparison of these two results. Cost and cost-effectiveness of zinc and vitamin A have been reported in the literature. Although the outcome measures are often disability-life-years, the costs have been presented separately. The financial cost of zinc in the treatment of diarrheal morbidity was \$14 per child<sup>40</sup>. A recent estimation of global costs of Vitamin A capsule delivered ranged from \$0.45 to \$2.25<sup>41</sup>. Based on our most conservative estimates, the cost per child and cost per sachet were \$8.16 and \$0.27 respectively.

Our data and the comparisons made with other studies should be interpreted in light of the existing limitations. Our cost estimates, for the majority, are only as sound as the recall of key activities, and their durations, by the KSHRSP and MOH staff, VHCs and mothers involved in the program. The results of this cost-effectiveness analysis will not be immediately comparable to studies that have used the DALY or other health valuations as an outcome. Further, in applying the methodology used by Horton and Ross (2003) it is understood that this method is based on several assumptions to arrive at a final formula and data are not available to support all links made between IDA in childhood and per capita productivity. It is not clear whether Horton and Ross's (2003) formula applies to both infants and young children. Further, this

methodology was used on country level data and further assumptions will have to be made to relate the programme level results from the KHRSP Sprinkles project data to these calculations. However, all these factors should be taken into account when applying this methodology and results interpreted accordingly.

#### ***4.5 CONCLUSIONS***

We found that using a weekly dose of iron as Sprinkles home-based fortification to treat or prevent anemia to be cost-effective compared to other nutrition interventions.

There is a need for more studies evaluating the cost-effectiveness of increasing hemoglobin levels using Sprinkles as well as other forms of home-based fortification or iron supplementation. This can lead to a fuller examination of the comparative cost-effectiveness of reducing or preventing anemia in pre-school children. This will present countries with a choice of affordable intervention strategies that they may adapt to address their specific micronutrient problems.

This analysis allows for a comparison with other CEAs done that relate to the cost-effectiveness of improving hemoglobin levels. The end goal of this analysis was to inform decision makers' choice regarding the use of Sprinkles in a programmatic setting to improve hemoglobin levels in children. Given this purpose a CEA was sufficient.

## REFERENCES

1. McLean E, Egli I, Cogswell M, de Benoist B, Wojdyla D. Worldwide prevalence of anemia in preschool aged children, pregnant women and non-pregnant women of reproductive age. In: Kraemer K, Zimmerman MB, editors. Nutritional anemia. Basel: Sight and Life Press, 2007. p. 1-12.
2. Lutter C, Rivera J. Nutritional status of infants and young children and characteristics of their diets. *J Nutr* 2003; 133:2941S-9S.
3. Lutter C, Dewey K. Proposed nutrient composition for fortified complementary foods. *J Nutr* 2003; 133:3011S-20S.
4. Gibson R, Ferguson E, Lehrfeld J. Complementary foods for infant feeding in developing countries: their nutrient adequacy and improvement. *Eur J Clin Nutr* 1998; 52:764-70.
5. Trowbridge T. Prevention and Control of Iron deficiency: Priorities and Action Steps. *J Nutr* 2002; 132:880S-882S.
6. Yip R. Prevention and control of iron deficiency in developing countries. *J Nutr* 2002; 132:802S-5S.
7. WHO/UNICEF/UNU. Iron deficiency anaemia: assessment, prevention and control. Geneva: World Health Organization, 2001.
8. Schlutink W, Gross R. Iron Deficiency Alleviation in Developing Countries. *Nutr Res Rev* 1996; 9:281-293.
9. Yip R. Iron supplementation: country level experiences and lessons learned. *J Nutr* 2002; 132:859S-61S.
10. Mora J. Iron supplementation: overcoming technical and practical barriers. *J Nutr* 2002; 132(4) Suppl: 853S-5S.
11. Stoltzfus R, and Dryefuss, M. Guidelines for the use of iron supplements to prevent and treat iron deficiency anaemia. Washington DC: ISLI Press, 1998.



12. Stoltzfus R, Dryefuss M. Iron deficiency: Global prevalence and consequences. *Food Nutr Bull* 2003; 24:S99-S103.
13. Micronutrient-Initiative. Anemia Prevention and Control: What Works? : Micronutrient Initiative, 2003.
14. Yip R. The challenge of improving iron nutrition: limitations and potentials of major intervention approaches. *Eur J Clin Nutr* 1997; 51: S16-15.
15. Zlotkin S, Antwi K, Schauer C, and GA Y. Home-fortification with iron and zinc sprinkles or iron sprinkles alone successfully treats anemia in infants and young children. *J Nutr* 2003; 133:1075-80.
16. Zlotkin S, Schauer C, Christofides A, Sharieff W, Tondeur M, S. Micronutrient sprinkles to control childhood anaemia. *Plos Med* 2005; 2:1.
17. Zlotkin S, Christofides A, Hyder S, Schauer C, Tondeur M. Controlling iron deficiency anemia through the use of home-fortified complementary foods. *Ind J of Ped* 2004; 71:1015-9.
18. Larey S, Adu-Afarwuah A, Brown K, Zlotkin S, Dewey K. Randomized comparison of 3 types of micronutrient supplements in Ghanaian Infants. Global Consultation on the Use of Paediatric Multiple Micronutrient Preparations in Emergencies. Panama City, Panama, 2005.
19. Christofides A, Zlotkin S, Schauer C. Impact of Micronutrient Sprinkles for the treatment and prevention of Iron Deficiency in Canadian First nations and Inuit Infants 4-18 months old. FASEB Experimental Biology Conference. San Diego, USA, 2003.
20. Martini E, Foote D, dePee S, et al. Efficacy of Sprinkles Home Fortification to Reduce Anemia and Micronutrient Deficiencies in Young Children in Indonesia. International Nutritional Anemia Consultative Group. Lima Peru, 2004.
21. Agostoni C, Giovannini M, Sala D, Uselli M, Livio L, Francescato G, Braga M, Riva E, Martiello A, Colombo C, Marangoni F, Galli C. Double-blind, placebo-controlled trial comparing effects of supplementation of two micronutrient sprinkles on fatty acid status in Cambodian infants. *J Pediatr Gastroenterol Nutr* 2007 Jan; 44(1): 136-42

22. Ruel M, Menon P, Loechl C, Pelto G. Donated fortified cereal blends improve the nutrient density of traditional complementary foods in Haiti, but iron and zinc gaps remain for infants. *Food Nutr Bull* 2004;25:361-76.
23. World-Vision. Effectiveness of Home-based Fortification With Sprinkles in Integrated Nutrition Program to Address Rickets and Anemia. Mongolia 2005.
24. Gold M, Siegel J, Russell L, Weinstein M. Cost-Effectiveness in Health and Medicine, New York: Oxford University Press, 1996.
25. Haddix A, Teutsch S, Corso P. Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation, New York: Oxford University Press 2002.
26. WHO. Making Choices in Health: WHO Guide to Cost-effectiveness Analysis. Geneva, Switzerland: World Health Organization, 2003.
27. R Baltussen, C Knai, M Sharan. Iron fortification and iron supplementation are cost-effective interventions to reduce iron deficiency in four subregions of the world *J Nutr* 2004;134.
28. Stoltzfus R, Mullany L, Black R. Iron deficiency anaemia. In: Ezzati M, Lopez A, Rodgers A, Murray C., eds. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. I. World Health Organization; Geneva: 2004. pp. 163–209.
29. European Observatory on Health Care Systems, EOHCS . Health care systems in transition, Romania. Copenhagen, Denmark: WHO, Regional Office for Europe. 2000.
30. World Bank. Enriching Lives: Overcoming Vitamin and Mineral Malnutrition in Developing Countries. Washington, DC: World Bank. 1994.
31. Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, World Population Prospects: The 2006 Revision and World Urbanization Prospects: The 2005 Revision. <http://esa.un.org/unpp>.
32. Caulfield L, Richard S, Rivera J, Musgrove P, Black R. Stunting, Wasting, and Micronutrient Deficiency Disorders. Disease Control Priorities in Developing Countries (2nd Edition), ed. , 551-568. New York: Oxford University Press. 2006.

33. Horton, S. "Unit Costs, Cost-Effectiveness, and Financing of Nutrition Interventions." PHN Working Paper 952. World Bank, Human Development Department, Washington, D.C. 1992.
34. Levin M. A benefit-cost analysis of nutritional programs for anemia reduction. Washington DC: World Bank PHN Technical Note 85-12, 1986.
35. Alonzo M, Menéndez C, Font F, Kahigwa E, Kimario J, Mshinda H, Tanner M, Bosch-Capblanch X, Alonso P. Cost-effectiveness of iron supplementation and malaria chemoprophylaxis in the prevention of anaemia and malaria among Tanzanian infants. *Bull World Health Organ* 2000; 78(1): 97-107.
36. Sharieff W, Horton S, Zlotkin S. Economic gains of a home fortification program: evaluation of "Sprinkles" from the provider's perspective. *Can J Public Health* 2006 Jan-Feb; 97(1): 20-3.
37. Menon P, Ruel M, Loechl C, Arimond M, Habicht J, Peltó G, Michaud L. Micronutrient Sprinkles reduce anemia among 9- to 24-mo-old children when delivered through an integrated health and nutrition program in rural Haiti. *J Nutr* 2007 Apr; 137(4): 1023-30.
38. Brooker S, Kabatereine N, Fleming F, Devlin N. Cost and cost-effectiveness of nationwide school-based helminth control in Uganda: intra-country variation and effects of scaling-up. *Health Policy Plan* 2008 Jan; 23(1): 24-35.
39. Guyatt H, Brooker S, Kihamia C, Hall A, Bundy D. Evaluation of the efficacy of school-based anthelmintic treatments against anaemia in children in the United Republic of Tanzania. *Bull World Health Organ* 2001; 79(8): 695-703.
40. Lechtig A, Gross R, Paulini J, de Romañ D. Costs of the multimicronutrient multisupplementation program in Chiclayo, Peru. *Food Nutr Bull* 2006; 27(4) Suppl Peru: S151-9.
41. Patel A, Dhande L, Rawat M. Economic evaluation of zinc and copper use in treating acute diarrhea in children: A randomized controlled trial. *Cost Eff Resour Alloc*. 2003; 1: 7.
42. Neidecker-Gonzales O, Nestel P, Bouis H. Estimating the global costs of vitamin A capsule supplementation: a review of the literature. *Food Nutr Bull* 2007 Sep; 28(3): 307-16.

## CHAPTER 5

### CONCLUSIONS

At the foundation of this dissertation was the objective of understanding the resistant public health problem of anemia in Asia. The first study considered the definition of anemia in lifelong high-altitude residents, the second focused on identifying risk factors for anemia in pre-school children and the third evaluated the cost-effectiveness of treating or preventing anemia in Asian preschoolers. At the end of this process, the following conclusions can be made based on our findings at each stage:

1. There is not one universal model of how the hemoglobin concentrations of high-altitude natives vary at different altitudes. Continuing to apply Andean altitude corrections universally potentially over-estimates the prevalence of anemia of non-Andean high-altitude natives. Over-estimations of anemia prevalence can bias evaluations of programmatic efforts to treat anemia.
2. Similar to other parts of Asia, the prevalence of anemia in Kyrgyz pre-school children is high. Immediate actions to address this problem should include universal home-based fortification with Sprinkles for all children 6 to 24 months and increased nutrition education targeted to mothers of infants and young children at the local level. Nutrition education programs should be based on the WHO 2000 guidelines for the feeding and nutrition of infants and young children in the European region and former Soviet countries. Emphasis should be on the correct and timely introduction of appropriate foods for infants and young children.
3. Home-based fortification with Sprinkles is cost-effective strategy the can be scaled up to prevent and treat anemia in pre-school children in Kyrgyzstan as well as other countries in Asia.

## **APPENDIX A:**

### **COST LIST**

**Fixed Costs:** These costs remain constant even as activity intensity varies

Facilities costs

- Rent,
- Maintenance
- Storage
- Transportation and travel expenses

Personnel Costs (based on yearly units of calculations)

- Support staff
- Administrative staff
- Volunteers
- Outside consultants

Finalization of Protocol

- Meeting with project staff
- Field visits
- Conference Calls
- Electronic communications

Registration Cost of Sprinkles by MOH

- Applications, Meetings( Time and money cost)

Cost of Information Campaign

- Materials
- Time of VHCs
- Per Diem for VHCs
- Advertisements

Baseline survey

- Staff per diem ( trainers and trainees)
- Staff Time ( Trainers and trainees)
- Training
- Materials for Training
- Materials for the execution of survey
- Cost of Time for execution of survey

Distribution of Sprinkles to homes

- Travel time for FGP/FAP
- Travel Cost for FGP/FAP
- Time spent during home visits
- Frequency of home visits
- Preparation time for home visits

Final survey (post-intervention)

Dissemination of the pilot project results

Planning and development of national programme

**Variable Costs:** Costs that change as level of activity changes(1)

Participant Costs

- Travel

Cost of Sprinkles

- Production
- Export
- Import ( taxes)
- Freight

Personnel Costs (based on hourly units of calculations)

- Support staff
- Administrative staff
- Volunteers
- Outside consultants

Supplies & miscellaneous

- Office supplies
- Computers
- Medical Supplies

Training Costs

- Manual development
- Training time
- Training costs ( materials, per diem, space rental)
- Community Action training
  - Development of training modules and monitoring tools

1. Haddix A, Teutsch S, Shaffer P, Dunet D. Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation. New York, 1996.